C/O PAULA

Access DB# 97097

# SEARCH REQUEST FORM

## Scientific and Technical Information Center

Requester's Full Name: *Maury Audet* Examiner #: *79808* Date: 6/22/03
Art Unit: *1654* Phone Number: *305-5039* Serial Number: 09/734583
Mail Box & Bldg/Room Locat.: CM1-*11D13; 11D04* Results Format Preferred: *PAPER*

**If more than one search is submitted, please prioritize searches in order of need.**

**********

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: ~~12/13/00~~ 6 60 w/ [BIBSHEET SHOWS EARLIER CIP DATES BACK TO 6/14/99 BUT STRUCTURES WERE NEW @ 12/13/00 FILING

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

1) Please search CLAIM 15, starting w/ elected specie (8th of 10 listed): Phe(CS)-Cyp*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(3Br)(Benzo)

2) If do not find structure above, please search other 9/10 structures in claim 15 [all 7-9 mers].

* NOTE: Core 4-mer running through all 10 structures (Phe-Trp-Trp-Lys

3) Please do Inventor search alongside.

TX, MAURY

WRONG ERROR Thru out

* All peptides are CYCLICIZED (not linear). But if any linear show up, include in as well in search request.
* All are analog of 14-mer somatostatin

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**STAFF USE ONLY**

Searcher: Sheppard
Searcher Phone #: 308-4499
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: 6/20/03
Searcher Prep & Review Time: _____
Clerical Prep Time: _____
Online Time: _____

**Type of Search**

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

**Vendors and cost where applicable**

STN _____
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (8-01)

## List of Amino Acid Abbreviations Annotated as "Xxx"

| Three letter abbr. | Name |
|---|---|
| Aaa | alpha-amino acid |
| Aad | 2-aminoadipic acid (2-aminohexanedioic acid) |
| Aan | alpha-asparagine |
| Abu | 2-aminobutanoic acid |
| Aca | 2-aminocapric acid (2-aminodecanoic acid) |
| Agn | alpha-glutamine |
| Aib | alpha-aminoisobutyric acid (2-aminoalanine) |
| Apm | 2-aminopimelic acid (2-aminoheptanedioic acid) |
| App | gamma-amino-beta-hydroxybenzenepentanoic acid |
| Asu | 2-aminosuberic acid (2-aminooctanedioic acid) |
| Aze | 2-carboxyazetidine |
| Bal | beta-alanine |
| Bas | beta-aspartic acid |
| Bly | 3,6-diaminohexanoic acid (beta-lysine) |
| Bua | butanoic acid |
| Bux | 4-amino-3-hydroxybutanoic acid |
| Cap | gamma-amino-beta-hydroxycyclohexanepentanoic acid) |
| Cit | N5-aminocarbonylornithine |
| Cya | 3-sulfoalanine |
| Dab | 2,4-diaminobutanoic acid |
| Dpm | diaminopimelic acid |
| Dpr | 2,3-diaminopropanoic acid |
| Dsu | 2,7-diaminosuberic acid (2,7-diaminooctanedioic acid) |
| Edc | S-ethylthiocysteine |
| Ggu | gamma-glutamic acid |
| Gla | gamma-carboxyglutamic acid |
| Glc | hydroxyacetic acid (glycolic acid) |
| Glp | pyroglutamic acid |
| Har | homoarginine |
| Hcy | homocysteine |
| Hhs | homohistidine |
| Hiv | 2-hydroxyisobutyric acid |
| Hse | homoserine |
| Hva | 2-hydroxypentanoic acid |
| Hyl | 5-hydroxylysine |
| Hyp | 4-hydroxyproline |
| Inc | 2-carboxyoctahydroindole |
| Iqc | 3-carboxyisoquinoline |
| Iva | isovaline |
| Lac | 2-hydroxypropanoic acid (lactic acid) |
| Maa | mercaptoacetic acid |
| Mba | mercaptobutanoic acid |
| Mhp | 4-methyl-3-hydroxyproline |
| Mpa | mercaptopropanoic acid |
| Nle | norleucine |
| Nty | nortyrosine |
| Nva | norvaline |
| Oaa | omega-amino acid |
| Orn | ornithine |

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FILE 'HCAPLUS' ENTERED AT 18:05:15 ON 19 JUN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 19 Jun 2003  VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003  (20030618/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L27                 STR
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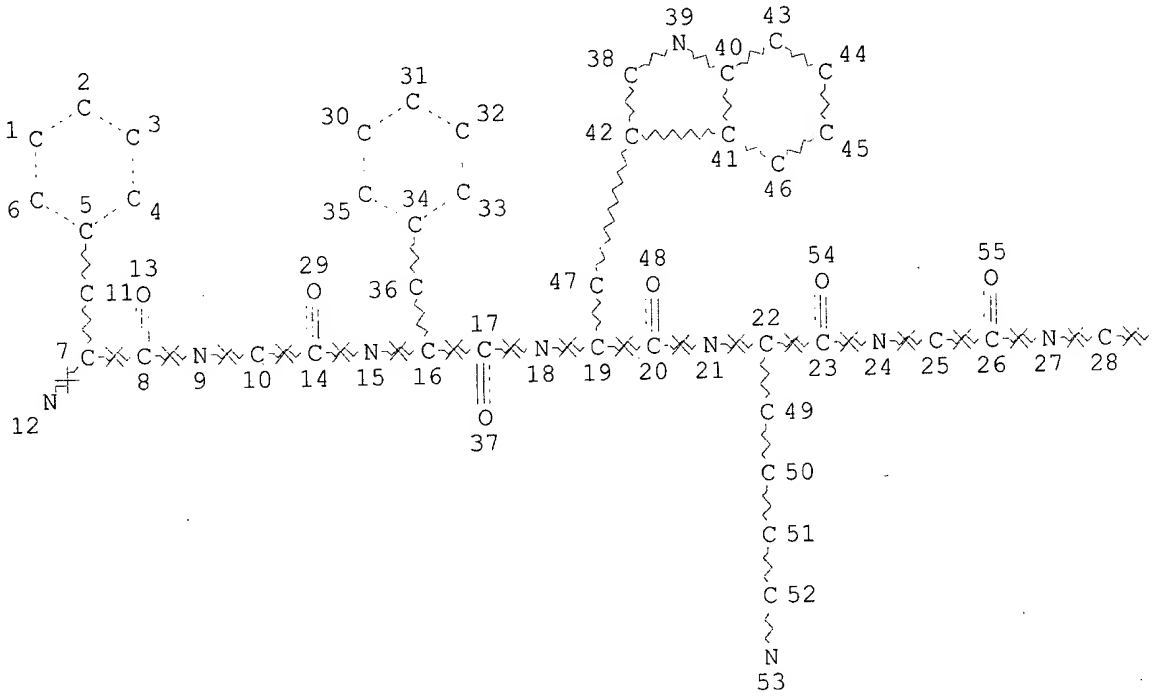

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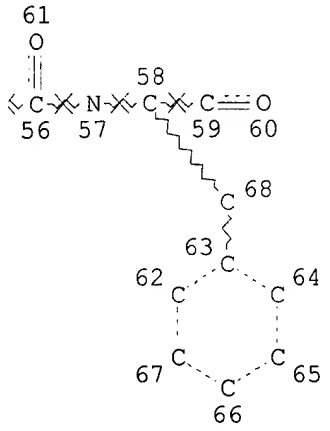


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DEFAULT ECLEVEL IS LIMITED

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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 68

STEREO ATTRIBUTES: NONE
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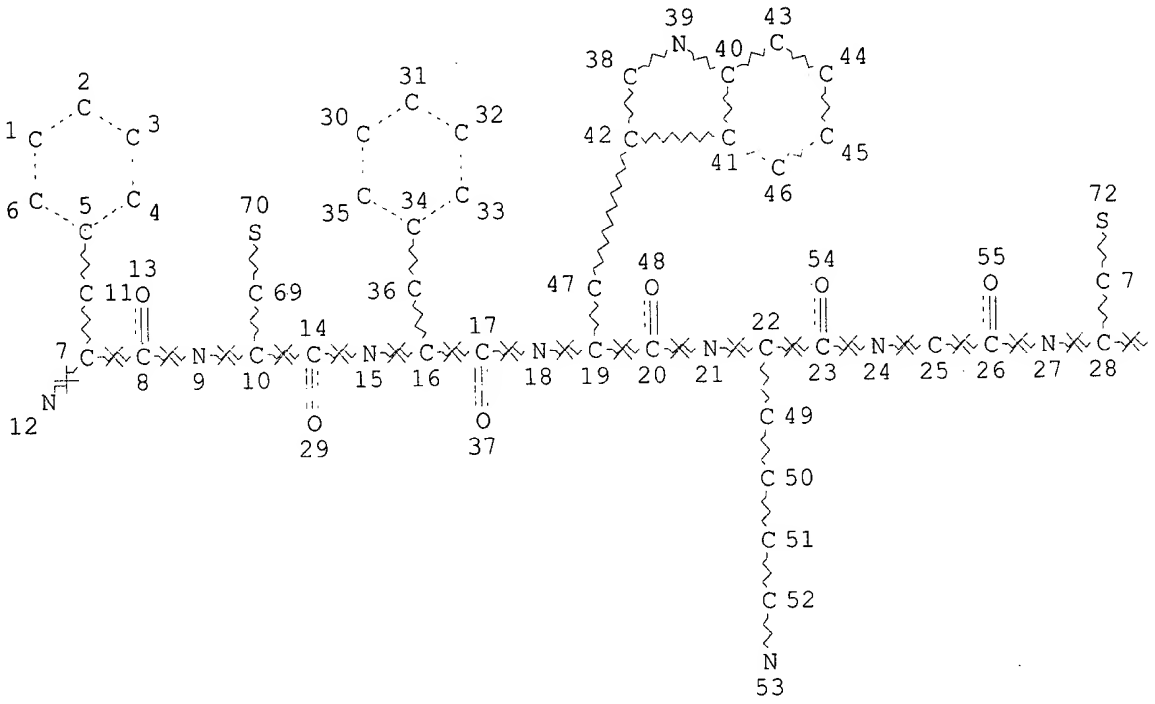
L32 STR



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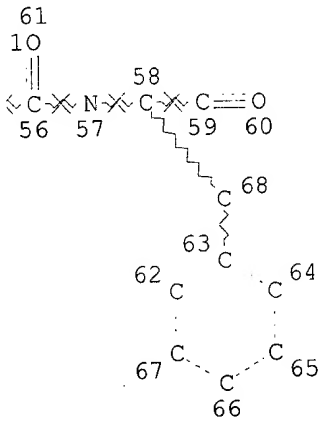

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  72

STEREO ATTRIBUTES: NONE
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L34            8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33


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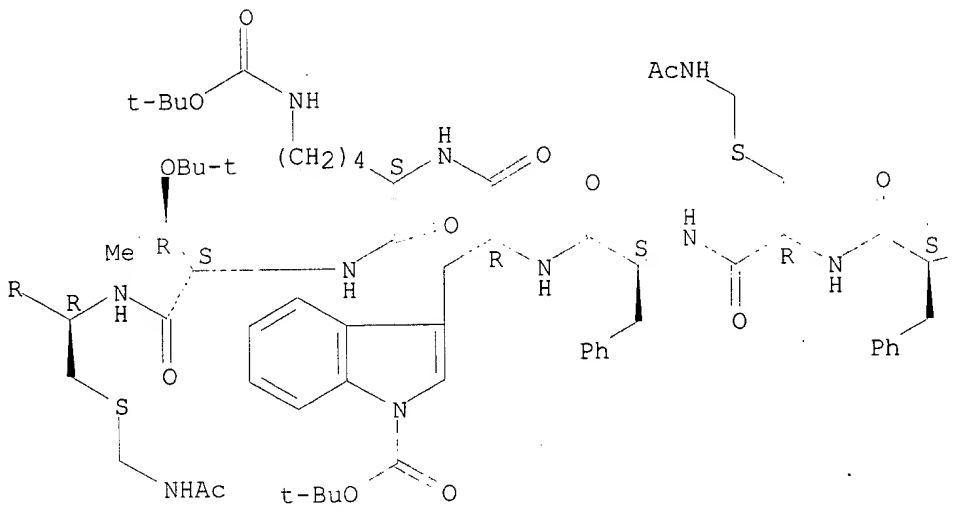
=> d ibib abs hitstr l34 1-8

L34  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2001:827035  HCAPLUS
DOCUMENT NUMBER:         136:210716
TITLE:                   A bicyclic and Hsst2 selective somatostatin analogue:
                         design, synthesis, conformational analysis and binding
AUTHOR(S):               Falb, Eliezer; Salitra, Yoseph; Yechezkel, Tamar;
                         Bracha, Moshe; Litman, Pninit; Olender, Roberto;
                         Rosenfeld, Rakefet; Senderowitz, Hanoch; Jiang,
                         Shaokai; Goodman, Murray
CORPORATE SOURCE:        Peptor Ltd., Rehovot, 76326, Israel
SOURCE:                  Bioorganic & Medicinal Chemistry (2001), 9(12),
                         3255-3264
                         CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER:               Elsevier Science Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   A backbone bridged and disulfide bridged bicyclic somatostatin analog,
     compd. 1 (PTR-3205), was designed and synthesized by solid-phase methodol.
     The binding of compd. 1 to the five different somatostatin receptors,
     expressed in CHO or COS-7 cells, indicate a high degree of selectivity
     towards hsstr2. The three-dimensional structure of this compd. has been
     detd. in DMSO-d6 and in water by 1H NMR and by mol. dynamics simulations.
     Similar backbone conformations were obsd. in both solvents. The authors
     have established direct evidence that the backbone of this bicyclic
     somatostatin analog assumes a 'folded' conformation in soln., where the
     lactam ring extends roughly in the plane of the .beta.-turn. The
     pharmacophoric region Phe-(d)-Trp-Lys-Thr of compd. 1 is in accord with
     that of both the Veber compd. L-363,301 (Merck) and sandostatin. The
     authors believe that the enhanced selectivity towards the hsst2 receptor,
     in comparison with other analogs, is due to its large hydrophobic region,
     composed of the lactam ring and the Phe side chains at positions 1 and 8.
IT   401912-42-3DP, resin bound
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (bicyclic and hsst2 selective somatostatin analog: design, synthesis,
     conformational anal. and binding)
RN   401912-42-3 HCAPLUS
```

CN L-Phenylalaninamide, N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-[4-oxo-4-(2-propenyloxy)butyl]-L-phenylalanyl-S-[(acetylamino)methyl]-L-cysteinyl-L-phenylalanyl-1-[(1,1-dimethylethoxy)carbonyl]-D-tryptophyl-N6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl-O-(1,1-dimethylethyl)-L-threonyl-S-[(acetylamino)methyl]-L-cysteinyl-N.alpha.-[3-[[(2-propenyloxy)carbonyl]amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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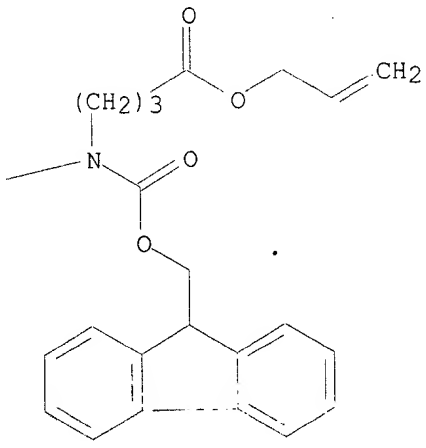

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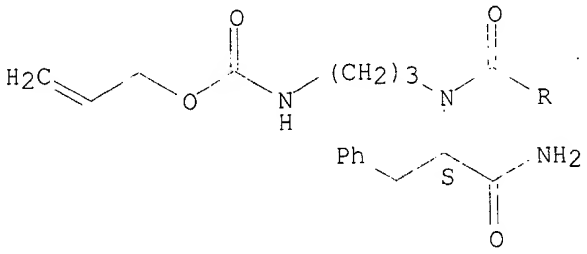


REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

poss.

L34 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:396636 HCAPLUS
DOCUMENT NUMBER: 131:208607
TITLE: Somatostatin receptor antagonists based on a mixed neuromedin B antagonist/somatostatin agonist
AUTHOR(S): Coy, David H.; Jain, Rahul; Murphy, William A.; Rossowski, Wojciech J.; Fuselier, Joseph; Taylor, John E.
CORPORATE SOURCE: Peptide Research Laboratories, Department of Medicine, Tulane University Medical Center, New Orleans, LA, 70112, USA
SOURCE: Peptides: Frontiers of Peptide Science, Proceedings of the American Peptide Symposium, 15th, Nashville, June 14-19, 1997 (1999), Meeting Date 1997, 526-529. Editor(s): Tam, James P.; Kaumaya, Pravin T. P. Kluwer: Dordrecht, Neth.
CODEN: 67UCAR
DOCUMENT TYPE: Conference
LANGUAGE: English

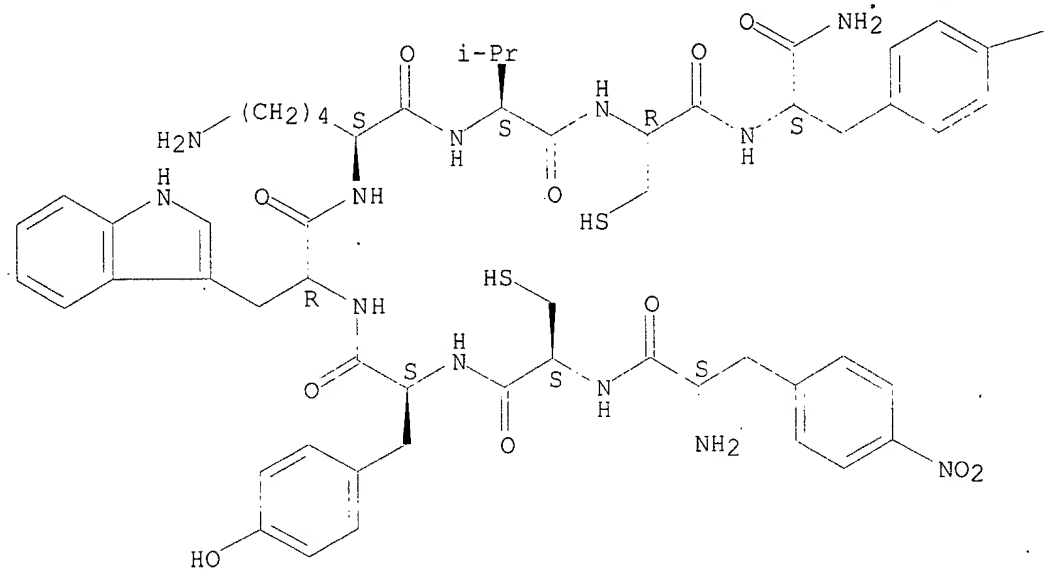
AB The somatostatin-antagonizing activities are reported for 19 analogs of D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH2. The high potencies in this type of type-2 receptor-specific somatostatin antagonists reside in the use of optimized arom. amino acid structures in positions 1 and 8. It was thought that the ability of these side-chains to form .pi.-.pi. complexes might offer an explanation for these results. However, mol. modeling studies in progress on these octapeptides suggest little possibility that this occurs. The D-Cys2 residue appears to force rotation of the position 1 side chains so that they protrude in the opposite direction to agonist side-chains with the remainder of the mol. being little changed. This may be the reason for their antagonist properties.

IT **243470-72-6**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(somatostatin receptor antagonists based on a mixed neuromedin B antagonist/somatostatin agonist)

RN 243470-72-6 HCAPLUS
CN L-Tyrosinamide, 4-nitro-L-phenylalanyl-D-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

OH

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:776177 HCAPLUS
DOCUMENT NUMBER: 128:33788
TITLE: Modulating the activity of hormones or their receptors - peptides, antibodies, vaccines and uses thereof
INVENTOR(S): Gerraty, Norman L.; Westbrook, Simon L.; Kingston, David J.
PATENT ASSIGNEE(S): Northstar Biologicals Pty. Ltd., Australia; Gerraty, Norman L.; Westbrook, Simon L.; Kingston, David J.
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9744352 | A1 | 19971127 | WO 1997-AU312 | 19970522 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9727575 | A1 | 19971209 | AU 1997-27575 | 19970522 |
| AU 738528 | B2 | 20010920 | | |
| CN 1226896 | A | 19990825 | CN 1997-196524 | 19970522 |

102(b)

| | | | | |
|---|---|---|---|---|
| BR 9709038 | A | 20000104 | BR 1997-9038 | 19970522 |
| EP 1012171 | A1 | 20000628 | EP 1997-921529 | 19970522 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| NZ 332926 | A | 20000825 | NZ 1997-332926 | 19970522 |
| JP 2000512130 | T2 | 20000919 | JP 1997-541271 | 19970522 |
| NZ 337256 | A | 20010427 | NZ 1997-337256 | 19970522 |
| US 2002107187 | A1 | 20020808 | US 2001-758128 | 20010112 |
| US 2002169116 | A1 | 20021114 | US 2001-758426 | 20010112 |
| US 2002187925 | A1 | 20021212 | US 2001-758198 | 20010112 |
| US 2003045676 | A1 | 20030306 | US 2001-861661 | 20010522 |

PRIORITY APPLN. INFO.:

| | | |
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| AU 1996-9990 | A | 19960522 |
| NZ 1997-332926 | A1 | 19970522 |
| WO 1997-AU312 | W | 19970522 |
| US 1999-194218 | B3 | 19990205 |

AB This invention relates to immunogenic, non-naturally occurring peptides and immunol. reactive mols. derived from animal hormone, carrier protein, hormone binding protein or hormone receptor wherein the peptide is capable of eliciting antibodies to modulate the activity of hormone or receptor in vivo. These peptides are based on e.g. portions of somatostatin, somatostatin receptors and insulin-like growth factor binding protein. Methods of modulating hormonal activity in an animal to increase prodn. of fiber or milk are disclosed. Compns. and vaccine comprising these peptides are also contemplated.

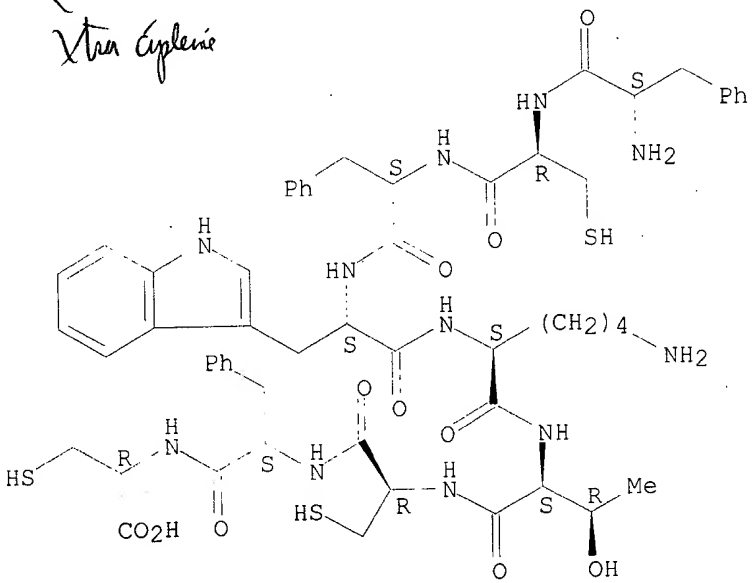
IT **199800-54-9P**

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptides, antibodies, vaccines for modulating hormones or hormone receptor activity in animal)

RN 199800-54-9 HCAPLUS

CN L-Cysteine, L-phenylalanyl-L-cysteinyl-L-phenylalanyl-(L)-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L34 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1989:450777 HCAPLUS
Correction of: 1987:96459

DOCUMENT NUMBER: 111:50777

Correction of: 106:96459

TITLE: Synthesis and evaluation of activities of octapeptide analogs of somatostatin

AUTHOR(S): Cai, Ren Zhi; Szoke, Balazs; Fu, Dadin; Redding, Tommie W.; Colaluca, John; Torres-Aleman, I.; Schally, Andrew V.

CORPORATE SOURCE: Med. Cent., Tulane Univ., New Orleans, LA, 70146, USA

SOURCE: Pept.: Struct. Funct., Proc. Am. Pept. Symp., 9th (1985), 627-30
CODEN: 54ZNAJ

DOCUMENT TYPE: Conference

LANGUAGE: English

GI For diagram(s), see printed CA Issue.

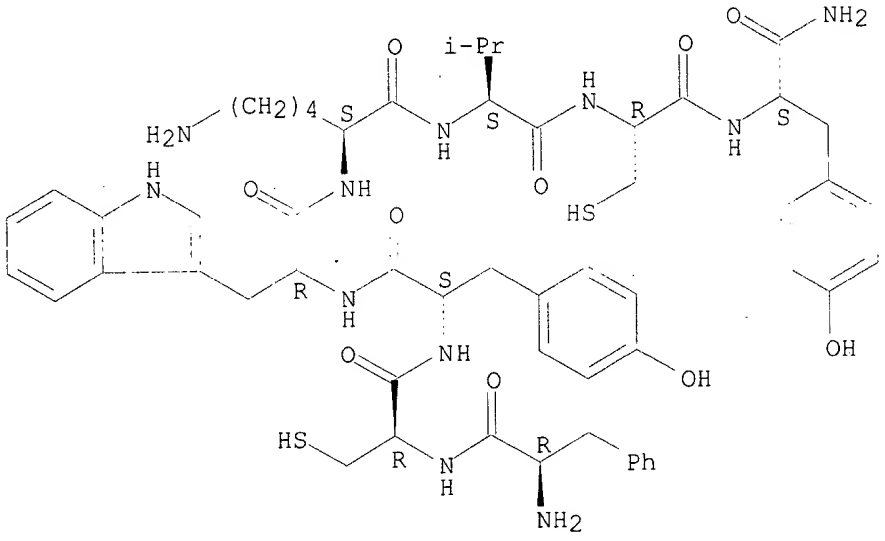
AB The growth hormone (GH) secretion inhibiting activity of somatostatin-14 and 17 octapeptide analogs was presented and related to structure. The most active compd. RC121 (I), was 200-fold more inhibitory than somatostatin-14 on GH secretion. The ctivities of the analogs indicate the importance of the C- and N-terminal residues, esp. the C-terminal residue hydroxyl group. Other biol. activities of the analogs were also briefly discussed.

IT **103222-04-4**
RL: BIOL (Biological study)
(growth hormone release inhibition by, structure in relation to)

RN 103222-04-4 HCAPLUS

CN L-Tyrosinamide, D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L34 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1987:515974 HCAPLUS

DOCUMENT NUMBER: 107:115974

TITLE: Biologically active lysine-containing octapeptides

INVENTOR(S): Schally, Andrew V.; Cai, Ren Zhi

PATENT ASSIGNEE(S): Tulane Educational Fund, Inc., USA

SOURCE: Eur. Pat. Appl., 33 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| EP 203031 | A2 | 19861126 | EP 1986-810174 | 19860415 |
| EP 203031 | A3 | 19880921 | | |
| EP 203031 | B1 | 19920729 | | |
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| US 4650787 | A | 19870317 | US 1985-727105 | 19850425 |
| US 4725577 | A | 19880216 | US 1986-843539 | 19860328 |
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| AU 8656338 | A1 | 19861030 | AU 1986-56338 | 19860417 |
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| CA 1333646 | A1 | 19941220 | CA 1986-507490 | 19860424 |
| JP 61293997 | A2 | 19861224 | JP 1986-97834 | 19860425 |
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| | | | EP 1986-810174 | 19860415 |

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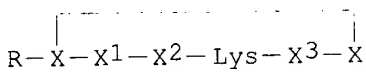


I

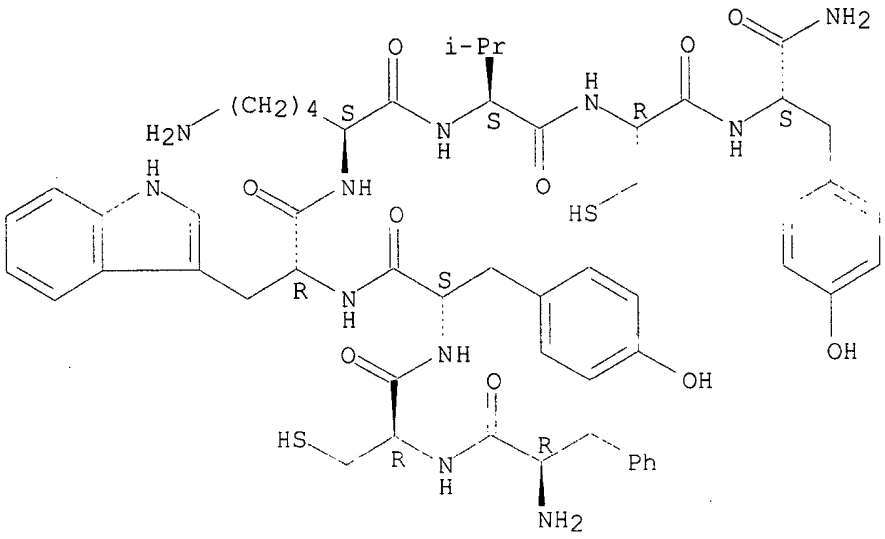
AB The octapeptide somatostatin analogs (I; R = (acetylated) L-, D- or DL-amino acid residue selected from H-Ala, H-Val, H-Phe, p-chlorophenylalanyl, H-Trp,H-Pro, H-Ser, H-Thr, H-Tyr, H-Glu, H-.beta.-Ala, H-Abu, MeAla, 5-halotryptophanyl; R1 = L-, D-, or DL-amino acid amide residue selected from Thr-NH2, Val-NH2, (hydroxy)Pro-NH2, Ser-NH2, 5-fluoro- or formyltryptophanamide residue, Ala-NH2, Gly-NH2, MeAla-NH2; X, X4 = L- or D- Cys, Abu, Asp, Lys; X1 = Phe, Tyr; X2 = L-, D-, or DL-5-halotryptophan residue; X3 = Thr, Val; Abu = .alpha.-aminobutyric acid residue)and pharmaceutically acceptable salts, useful as growth hormone inhibitors, for treatment of gastrointestinal disorders, cancer therapy, and the management of diabetes, were prepd. by the solid-phase method using a benzhydrylamine resin. I in vivo were more potent inhibitors of growth hormone and insulin release than somatostatin-14 in rats.

IT **103222-04-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and cyclization of, somatostatin analog from)

RN 103222-04-4 HCAPLUS

CN L-Tyrosinamide, D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



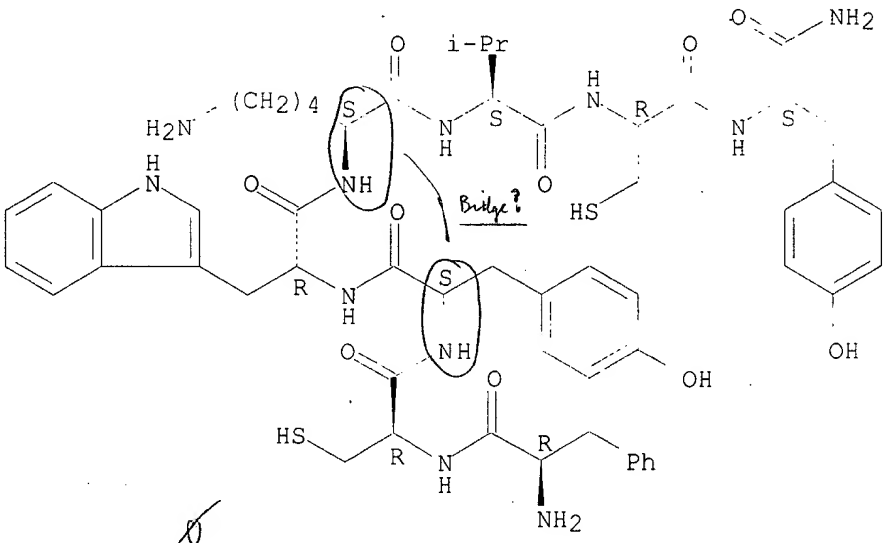
L34 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:472825 HCAPLUS
DOCUMENT NUMBER: 105:72825
TITLE: Synthesis and biological activity of highly potent octapeptide analogs of somatostatin
AUTHOR(S): Cai, R. Z.; Szoke, B.; Lu, R.; Fu, D.; Redding, T. W.; Schally, A. V.
CORPORATE SOURCE: Sch. Med., Tulane Univ., New Orleans, LA, 70146, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1986), 83(6), 1896-900
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the search for selective and long-acting analogs of somatostatin, nearly 200 compds. were synthesized by solid-phase methods, purified, and tested biol. Among these octapeptides, some contained N-terminal D-Phe, Ac-D-Phe, or AcPhe followed by hexapeptide sequences Cys-Phe-D-Trp-Lys-Thr-Cys or Cys-Tyr-D-Trp-Lys-Val-Cys and Thr-NH2 or Trp-NH2 as C-terminal residues. (Cyclo 2-7)-D-Phe-Cys-Try-D-Trop-Lys-Val-Cys-Thr-NH2 (I) [99660-13-6] and (cyclo 2-7)-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH2 (II) [103222-11-3] were 177 times and 113 times more potent, resp., than somatostatin in tests for inhibition of growth hormone [9002-72-6] release. These 2 octapeptides contg. tyrosine and valine in positions 3 and 6, resp., were more active and more selective than their Ph-3 and Thr-6 counterparts, (cyclo 2-7)-D-Phe-Cys-Phe-D-Trp-Lys-thr-Cys-Thr-NH2 [99685-66-2] and (cyclo 2-7)-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH2 [103222-10-2]. I was also .apprx.6 times more potent than its L-Trp-4 diastereoisomer [103222-07-7]. The analogs I, and II showed a prolonged duration of action and inhibited growth hormone release for at least 3 h. Analogs of both Phe-3/Thr-6 and Tyr-3/Val-6 classes also suppressed the release of insulin [9004-10-8] and glucagon [9007-92-5] in rats and pentagastrin-induced secretion of gastric acid in dogs, but their potencies in these tests were much smaller than the growth-hormone-release inhibitory activity. Some of these analogs possessed antitumor activities as shown by the inhibition of growth of animal models of prostate, mammary, and ductal pancreatic tumors.

IT **103222-04-4 103527-39-5 103548-91-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(growth hormone secretion inhibition by, mol. structure in relation to)

RN 103222-04-4 HCAPLUS
CN L-Tyrosinamide, D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl- (9CI) (CA INDEX NAME)

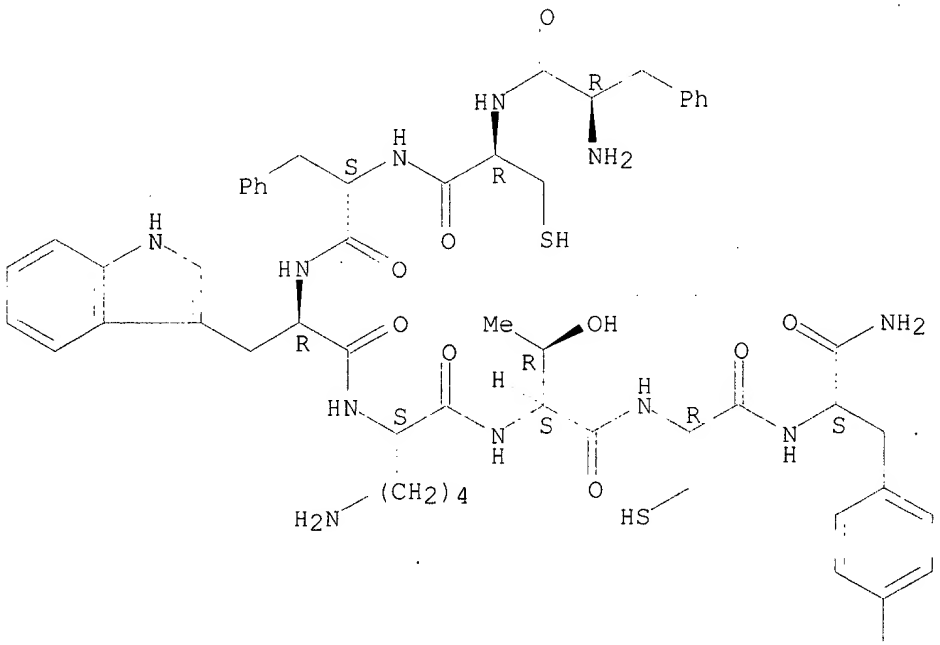
Absolute stereochemistry.




RN 103527-39-5 HCAPLUS
CN L-Tyrosinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



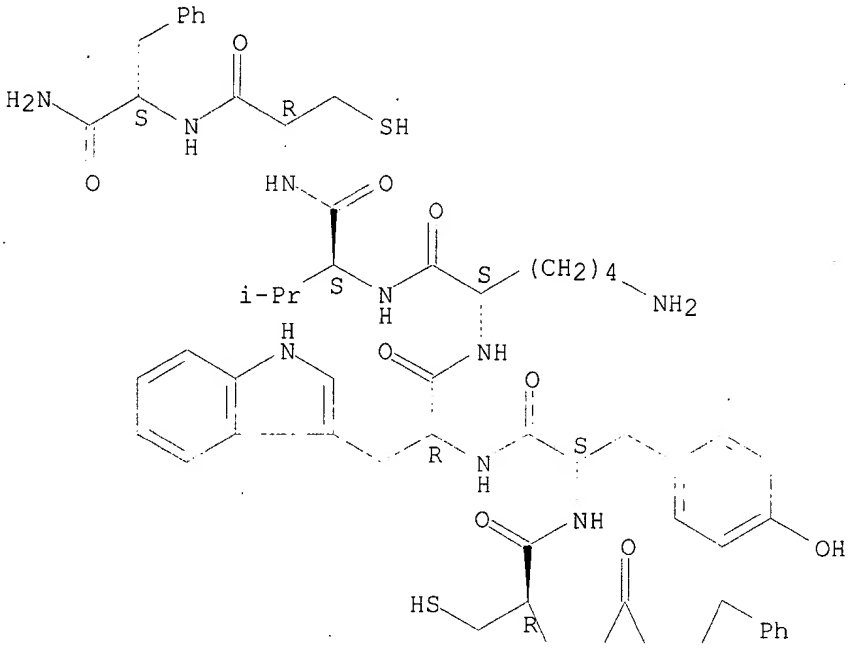
PAGE 2-A

OH

RN 103548-91-0 HCAPLUS
CN L-Phenylalaninamide, D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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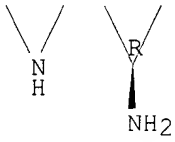


L34 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:438833 HCAPLUS
DOCUMENT NUMBER: 101:38833
TITLE: Nonapeptide anti-secretory agents
INVENTOR(S): Sarantakis, Dimitrios
PATENT ASSIGNEE(S): American Home Products Corp., USA
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 4440904 | A | 19840403 | US 1983-462168 | 19830131 |

PRIORITY APPLN. INFO.: US 1983-462168 19830131

GI For diagram(s), see printed CA Issue.

AB Nonapeptides I (X = His, D-His, Lys, Arg; X1 = Phe, D-Phe, Tyr, Trp, Leu, Met, His, Glu, Asp; X2 = Phe, Tyr, Trp, Leu, Met; X3 = Trp, D-Trp; X4 = Thr, Val, NHCHEtCO; X5 = Phe, D-Phe, Tyr, Trp, Leu, Met, Ser, Thr) were prepd. as inhibitors of growth hormone (GH) release and anti-secretory agents which act as H2-receptor antagonists. Thus, Me3CO2C-His(CO2CH2Ph)-Tyr(CH2C6H3Cl2-2,6)-Cys(MBzl)-Phe-D-Trp-Lys(CO2CH2C6H4Cl-2)-Thr(CH2Ph)-Cys(MBzl)-Phe-O-resin (MBzl = CH2C6H4OMe-4) was prepd. by the solid-phase method and then it was resin cleaved and deblocked by HF/anisole and then oxidized by K3Fe(CN)6 to give nonapeptide II. II at 200 mg/kg inhibited GH release in rats with a potency similar to that of somatostatin; II at 2 mg/kg decreased gastric acid output in rats by 73%.

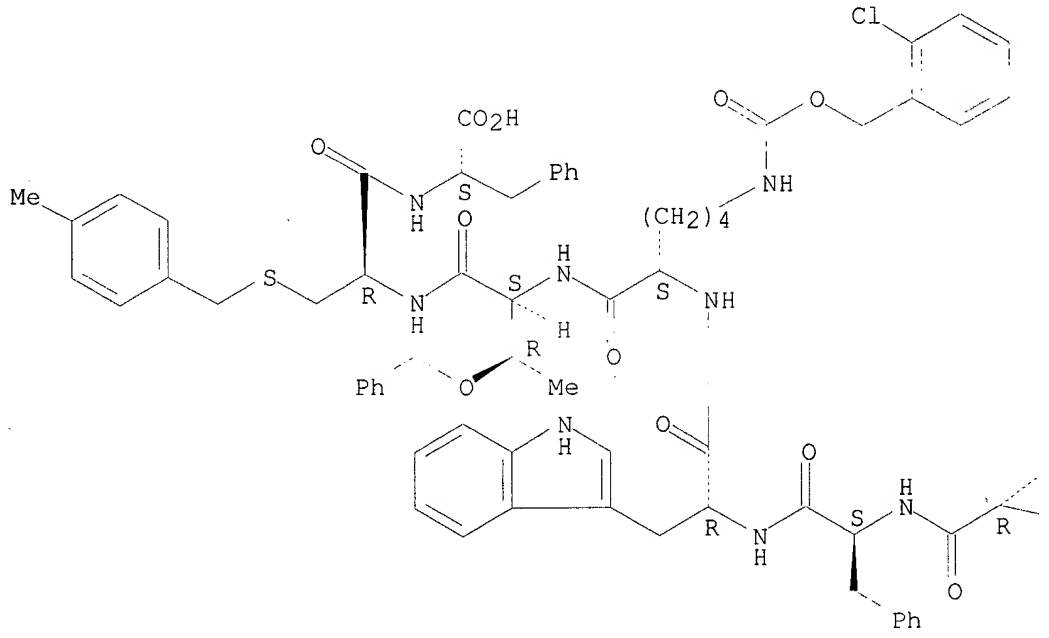
IT **90773-79-8DP**, resin-bound
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and resin cleavage-deblocking of)

RN 90773-79-8 HCAPLUS

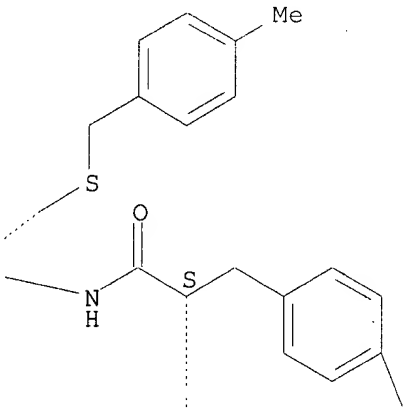
CN L-Phenylalanine, N-[N-[N-[N6-[[(2-chlorophenyl)methoxy]carbonyl]-N2-[N-[N-[N-[O-[(2,6-dichlorophenyl)methyl]-N-[N-[(1,1-dimethylethoxy)carbonyl]-1-[(phenylmethoxy)carbonyl]-L-histidyl]-L-tyrosyl]-S-[(4-methylphenyl)methyl]-L-cysteinyl]-L-phenylalanyl]-D-tryptophyl]-L-lysyl]-O-(phenylmethyl)-L-threonyl]-S-[(4-methylphenyl)methyl]-L-cysteinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

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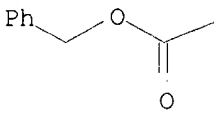
PAGE 2-A



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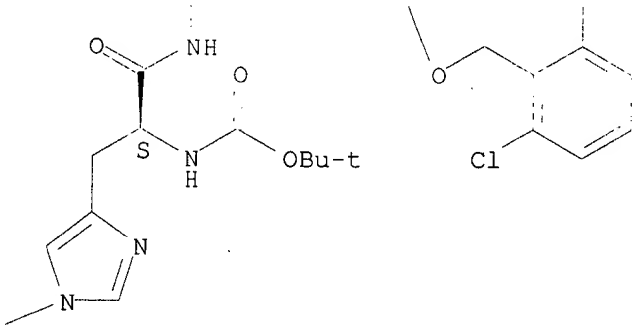


L34 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:587683 HCAPLUS
DOCUMENT NUMBER: 95:187683
TITLE: Octapeptides lowering growth hormone
INVENTOR(S): Sarantakis, Dimitrios
PATENT ASSIGNEE(S): American Home Products Corp., USA
SOURCE: U.S., 4 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 4282143 | A | 19810804 | US 1980-159327 | 19800613 |
| US 4328135 | A | 19820504 | US 1981-233813 | 19810212 |

PRIORITY APPLN. INFO.: US 1980-159327 19800613

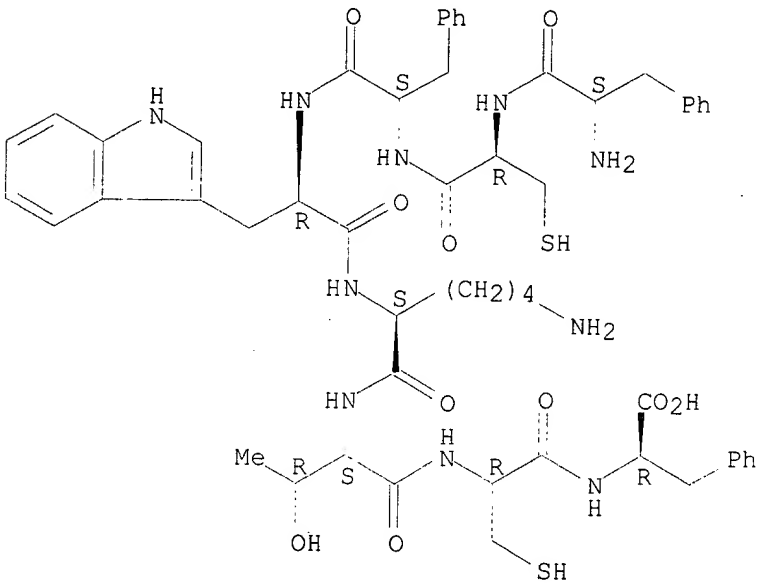
GI For diagram(s), see printed CA Issue.

AB R-Cys(R1)-X-X1-Lys-X2-Cys(R2)-R3 (I; R = H-Phe, H-D-Phe, PhCH2CH2CO; R1 = R2 = H, R1R2 = bond; X = Phe, Tyr, Trp, Met, Leu; X1 = Trp, D-Trp; X2 = Thr, Val, NHCHEtCO, Phe; R3 = Phe-OH, D-Phe-OH, NHCH2CH2Ph) were prepd. I inhibited the release of growth hormone (GH) without materially altering blood serum levels of glucagon or insulin. Thus, Me3CO2C-Phe-Cys(MBzl)-Phe-D-Trp-Lys(CO2CH2C6H4Cl-2)-Thr(CH2Ph)-Cys(MBzl)-D-Phe-OCH2-resin (MBzl = CH2C6H4OMe-p) was prepd. by the stepwise solid-phase method and then it was resin cleaved and deblocked by HF/anisole to give the linear octapeptide, which was cyclized by oxidn. with K3Fe(CN)6 to give octapeptide cyclic disulfide II. II at 20 .mu.g/kg (s.c.) lowered blood serum levels of GH in rats from 277 mg/mL to 56 ng/mL without significantly altering the levels of glucagon or insulin.

IT **79698-23-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and oxidative cyclization of)

RN 79698-23-0 HCAPLUS
CN D-Phenylalanine, N-[N-[N-[N2-[N-[N-(N-L-phenylalanyl-L-cysteinyl)-L-phenylalanyl]-D-tryptophyl]-L-lysyl]-L-threonyl]-L-cysteinyl]- (9CI) (CA INDEX NAME)

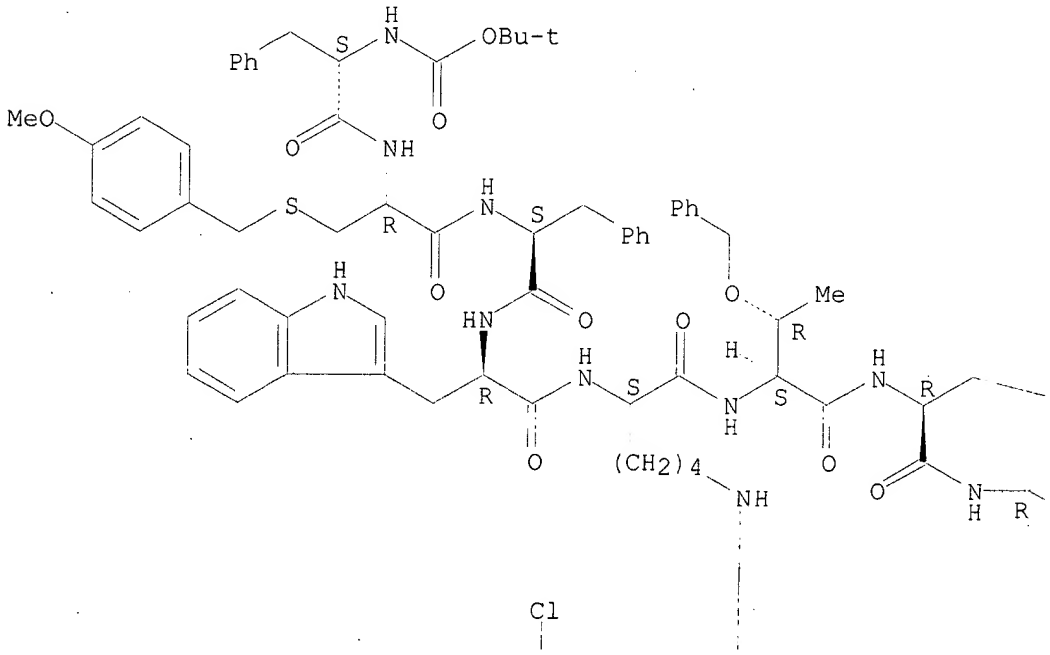
Absolute stereochemistry.



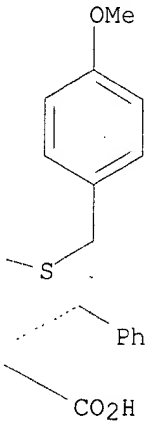
IT **79698-21-8DP**, resin-bound
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and resin-cleavage and deblocking of)
RN 79698-21-8 HCAPLUS
CN D-Phenylalanine, N-[N-[N-[N6-[[(2-chlorophenyl)methoxy]carbonyl]-N2-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-S-[(4-methoxyphenyl)methyl]-L-cysteinyl]-L-phenylalanyl]-D-tryptophyl]-L-lysyl]-O-(phenylmethyl)-L-threonyl]-S-[(4-methoxyphenyl)methyl]-L-cysteinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

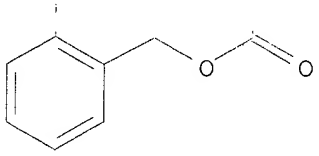
PAGE 1-A



PAGE 1-B




PAGE 2-A

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FILE LAST UPDATED: 01 May 1997 (19970501/UP)

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L35 0 L33

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STRUCTURE FILE UPDATES:   18 JUN 2003  HIGHEST RN 533863-98-8
DICTIONARY FILE UPDATES:  18 JUN 2003  HIGHEST RN 533863-98-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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FILE COVERS 1907 - 19 Jun 2003  VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003  (20030618/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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=> d stat que l38 nos
L27             STR
L29         221 SEA FILE=REGISTRY SSS FUL L27
L32             STR
L33           9 SEA FILE=REGISTRY SUB=L29 SSS FUL L32
L34           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33
L36          33 SEA FILE=REGISTRY ABB=ON  PLU=ON  FCFWKTCF/SQSP
L37          29 SEA FILE=REGISTRY ABB=ON  PLU=ON  L36 NOT L33
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L38 13 SEA FILE=HCAPLUS ABB=ON PLU=ON L37 NOT L34

=>
=>

=> d ibib fhitseq l38 1-13

L38 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:615640 HCAPLUS
DOCUMENT NUMBER: 137:165559
TITLE: Backbone cyclized radiolabelled somatostatin analogs
INVENTOR(S): Bonasera, Thomas A.; Livnah, Nurit; Yechezkel, Tamar; Salitra, Yoseph
PATENT ASSIGNEE(S): Peptor Ltd., Israel
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002062819 | A2 | 20020815 | WO 2002-IL91 | 20020204 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

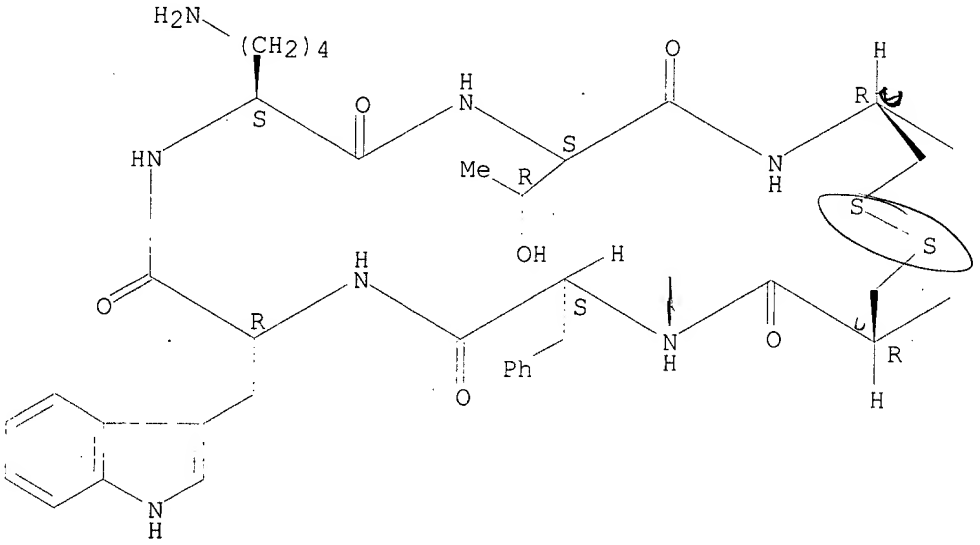
PRIORITY APPLN. INFO.: IL 2001-141276 A 20010205
OTHER SOURCE(S): MARPAT 137:165559
IT **446311-40-6DP**, complexes with Indium and DTPA
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(backbone cyclized radiolabeled somatostatin analogs as potential imaging and therapeutic agents)
RN 446311-40-6 HCAPLUS
CN L-Phenylalaninamide, glycyl-N-(3-carboxypropyl)-L-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-N.alpha.-(3-aminopropyl)-, (2.fwdarw.9)-lactam, cyclic (3.fwdarw.8)-disulfide (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 GFCFWKTCF

Absolute stereochemistry.

PAGE 1-A

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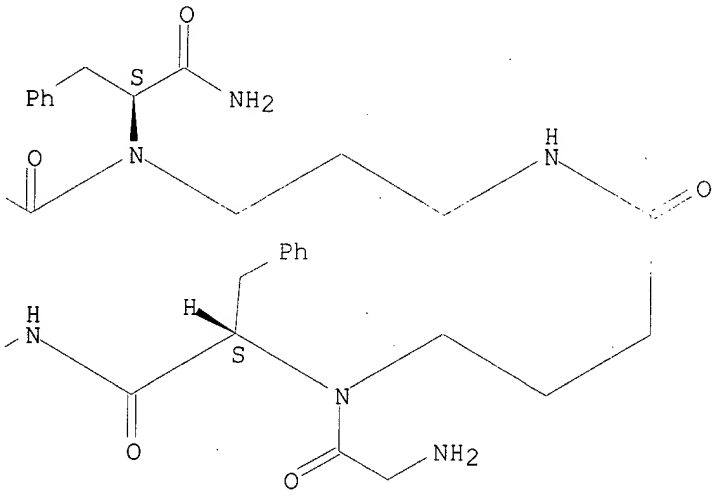



L38 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:332670 HCAPLUS
DOCUMENT NUMBER: 136:341003
TITLE: Preparation of conformationally constrained backbone cyclized somatostatin analogs
INVENTOR(S): Hornik, Vered; Afargan, Michel M.; Gellerman, Gary
PATENT ASSIGNEE(S): Israel
SOURCE: U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of Appl. No. PCT/IL99/00329.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2002052315 | A1 | 20020502 | US 2000-734583 | 20001213 |
| US 6051554 | A | 20000418 | US 1998-100360 | 19980619 |
| US 6355613 | B1 | 20020312 | US 1998-203389 | 19981202 |
| WO 9965508 | A1 | 19991223 | WO 1999-IL329 | 19990615 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 1998-100360 A2 19980619
US 1998-203389 A2 19981202
WO 1999-IL329 A2 19990615
US 1995-488159 A2 19950607
US 1995-569042 A2 19951207
US 1996-690609 A2 19960731

Diff #

OTHER SOURCE(S): MARPAT 136:341003
IT 252845-38-8P, PTR 3205
RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of conformationally constrained backbone cyclized somatostatin analogs)

APPLIC.

RN 252845-38-8 HCAPLUS
CN L-Phenylalaninamide, N-(3-carboxypropyl)-L-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-phenylalanyl-N.alpha.-(3-aminopropyl)-, (1.fwdarw.9)-lactam, cyclic (2.fwdarw.7)-disulfide (9CI) (CA INDEX NAME)

Disclosed in issued pat.

NTE modified (modifications unspecified)

SEQ 1 FCFWKTCFF

9

L38 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:65930 HCAPLUS
DOCUMENT NUMBER: 132:77604
TITLE: Modulation of hormonal responses in animals with peptide vaccines
INVENTOR(S): Gerraty, Norman L.; Westbrook, Simon L.; Kingston, David J.
PATENT ASSIGNEE(S): Northstar Biologicals Pty. Ltd., Australia
SOURCE: S. African, 137 pp.
CODEN: SFXXAB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| ZA 9710584 | A | 19980819 | ZA 1997-10584 | 19971125 |

PRIORITY APPLN. INFO.: ZA 1997-10584 19971125

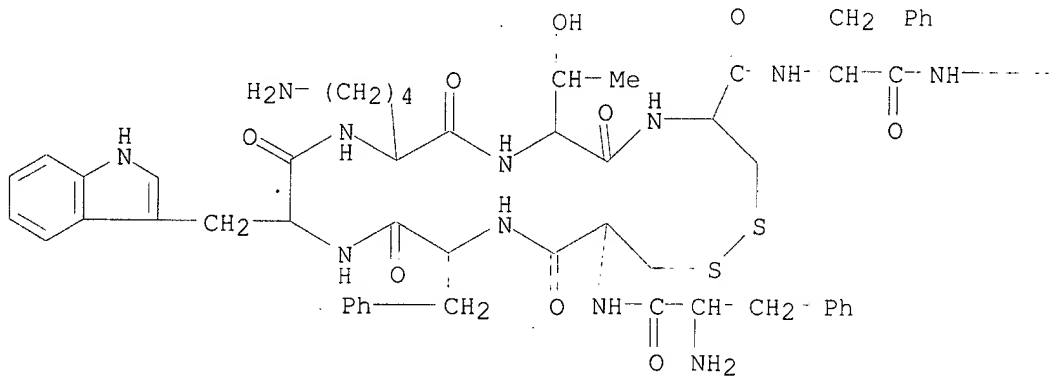
SAME AS IN OTHER 8

But earlier priority in other 1

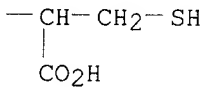
IT **253791-02-5**
RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); BIOL (Biological study); USES (Uses)
(immunization with peptides of animal hormones, their binding proteins, or receptors for immunol. control of endocrine function)
RN 253791-02-5 HCAPLUS
CN L-Cysteine, L-phenylalanyl-L-cysteinyl-L-phenylalanyl-L-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-phenylalanyl-, cyclic (2.fwdarw.7) disulfide (9CI) (CA INDEX NAME)

SEQ 1 FCFWKTCFC

PAGE 1-A



PAGE 1-B



L38 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:53668 HCAPLUS
DOCUMENT NUMBER: 132:108301
TITLE: Processes for coupling amino acids using bis(trichloromethyl) carbonate
INVENTOR(S): Fall, Elirezer; Yechezkel, Tamar; Salitra, Yoseph
PATENT ASSIGNEE(S): Peptor Ltd., Israel
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000002898 | A1 | 20000120 | WO 1999-IL378 | 19990711 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,

JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| CA 2334076 | AA | 20000120 | CA 1999-2334076 | 19990711 |
| AU 9946454 | A1 | 20000201 | AU 1999-46454 | 19990711 |
| AU 754560 | B2 | 20021121 | | |
| EP 1097164 | A1 | 20010509 | EP 1999-929678 | 19990711 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2002520331 | T2 | 20020709 | JP 2000-559127 | 19990711 |
| NZ 509304 | A | 20030131 | NZ 1999-509304 | 19990711 |
| US 2001007037 | A1 | 20010705 | US 2001-756223 | 20010109 |
| US 6512092 | B2 | 20030128 | | |

PRIORITY APPLN. INFO.: IL 1998-125314 A 19980712
WO 1999-IL378 W 19990711

OTHER SOURCE(S): CASREACT 132:108301

IT **255872-38-9P**, PTR 3205
RL: SPN (Synthetic preparation); PREP (Preparation)
(processes for coupling amino acids using bis(trichloromethyl) carbonate)

RN 255872-38-9 HCAPLUS

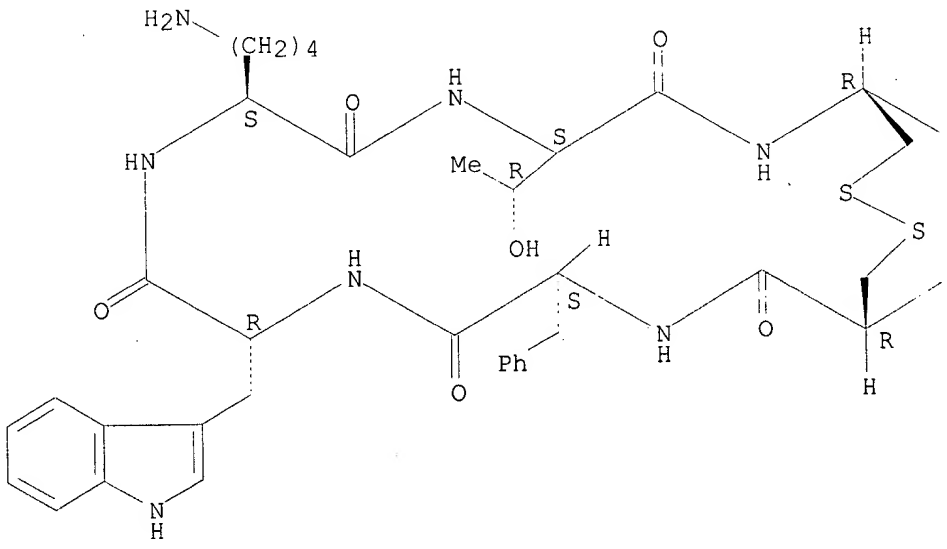
CN L-Phenylalaninamide, N-(3-carboxypropyl)-L-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-N.alpha.-(3-aminopropyl)-, (1.fwdarw.8)-lactam, cyclic (2.fwdarw.7)-disulfide (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

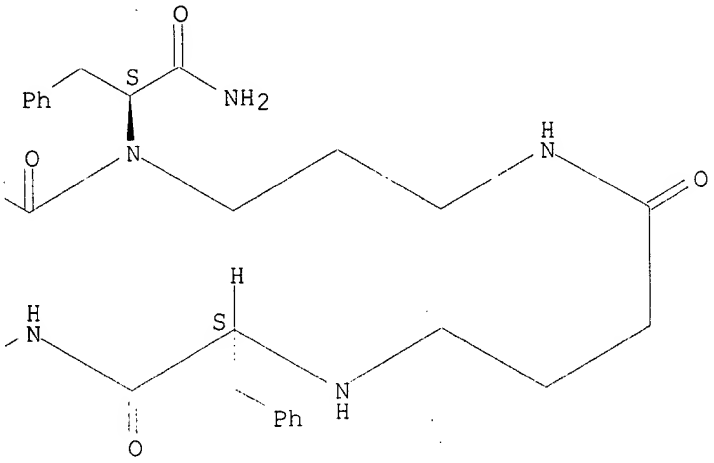
SEQ 1 FCFWKTCF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:811096 HCAPLUS
DOCUMENT NUMBER: 132:50250
TITLE: Preparation of conformationally constrained backbone cyclized somatostatin analogs
INVENTOR(S): Hornik, Vered; Afargan, Michel M.; Gellerman, Gary
PATENT ASSIGNEE(S): Peptor Ltd., Israel
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9965508 | A1 | 19991223 | WO 1999-IL329 | 19990615 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6051554 | A | 20000418 | US 1998-100360 | 19980619 |
| US 6355613 | B1 | 20020312 | US 1998-203389 | 19981202 |
| CA 2335488 | AA | 19991223 | CA 1999-2335488 | 19990615 |
| AU 9942884 | A1 | 20000105 | AU 1999-42884 | 19990615 |
| AU 747515 | B2 | 20020516 | | |
| EP 1085896 | A1 | 20010328 | EP 1999-957020 | 19990615 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002518339 | T2 | 20020625 | JP 2000-554387 | 19990615 |
| US 2002052315 | A1 | 20020502 | US 2000-734583 | 20001213 |

PRIORITY APPLN. INFO.: US 1998-100360 A 19980619
US 1998-203389 A 19981202

US 1995-488159 A2 19950607
US 1995-569042 A2 19951207
US 1996-690609 A2 19960731
WO 1999-IL329 W 19990615

OTHER SOURCE(S): MARPAT 132:50250
IT **252845-38-8P**, PTR 3205
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of conformationally constrained backbone cyclized somatostatin analogs)
RN 252845-38-8 HCAPLUS
CN L-Phenylalaninamide, N-(3-carboxypropyl)-L-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-phenylalanyl-N.alpha.-(3-aminopropyl)-, (1.fwdarw.9)-lactam, cyclic (2.fwdarw.7)-disulfide (9CI) (CA INDEX NAME)

APPLIC.

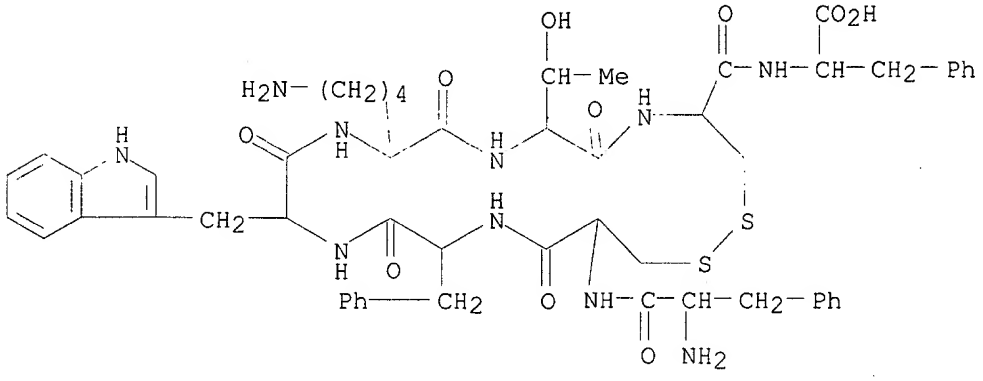
NTE modified (modifications unspecified)

SEQ 1 FCFWKTCFF

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:547527 HCAPLUS
DOCUMENT NUMBER: 107:147527
TITLE: Structure-activity studies of somatostatin analogs, substituted at positions 4 and 5
AUTHOR(S): Sarantakis, D.
CORPORATE SOURCE: Res. Div., Wyeth Lab., Philadelphia, PA, 19101, USA
SOURCE: Pept., Proc. Eur. Pept. Symp., 19th (1987), Meeting Date 1986, 535-8. Editor(s): Theodoropoulos, Dimitrios. de Gruyter: Berlin, Fed. Rep. Ger.
CODEN: 56ABA8
DOCUMENT TYPE: Conference
LANGUAGE: English
IT **79698-22-9**
RL: BIOL (Biological study)
(glucagon and growth hormone and insulin secretion inhibition by, structure in relation to)
RN 79698-22-9 HCAPLUS
CN D-Phenylalanine, L-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-, cyclic (2.fwdarw.7)-disulfide (9CI) (CA INDEX NAME)

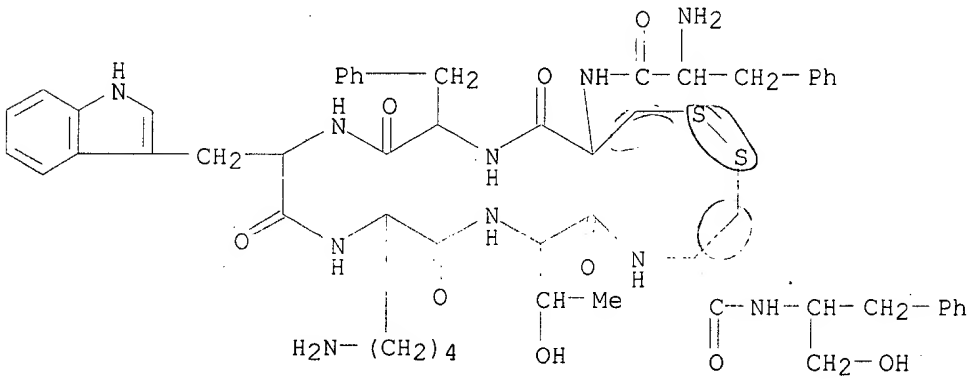
SEQ 1 FCFWKTCF



L38 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:770 HCAPLUS
DOCUMENT NUMBER: 106:770
TITLE: Chemistry and pharmacology of SMS 201-995, a long-acting octapeptide analog of somatostatin
AUTHOR(S): Pless, Janos; Bauer, Wilfried; Briner, Ulrich; Doepfner, Wolfgang; Marbach, Peter; Maurer, Richard; Petcher, Trevor J.; Reubi, Jean Claude; Vonderscher, Jacky
CORPORATE SOURCE: Preclin. Res. Dep., SANDOZ Ltd., Basel, CH-4002, Switz.
SOURCE: International Congress Series (1986), 683(Endocrinology '85), 319-33
CODEN: EXMDA4; ISSN: 0531-5131
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **79486-62-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(biol. activity of, mol. structure in relation to)
RN 79486-62-7 HCAPLUS
CN L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[1-(hydroxymethyl)-2-phenylethyl]- cyclic (2.fwdarw.7)-disulfide, (S)- (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 FCFWKTCF

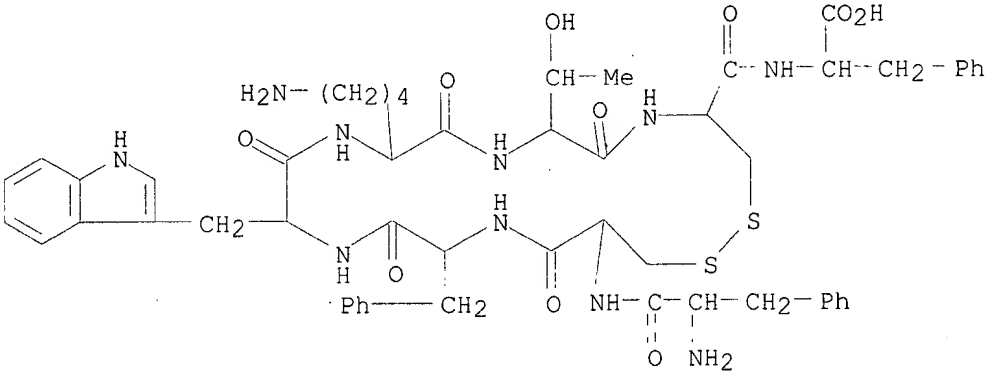


L38 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:449288 HCAPLUS
DOCUMENT NUMBER: 101:49288
TITLE: Octapeptides as antiulcer agents
INVENTOR(S): Lien, Eric L.
PATENT ASSIGNEE(S): American Home Products Corp., USA
SOURCE: U.S., 3 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 4443434 | A | 19840417 | US 1982-409255 | 19820818 |

PRIORITY APPLN. INFO.: US 1982-409255 19820818
IT **79698-22-9**
RL: BIOL (Biological study)
(ulcer treatment with)
RN 79698-22-9 HCAPLUS
CN D-Phenylalanine, L-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-, cyclic (2.fwdarw.7)-disulfide (9CI) (CA INDEX NAME)

SEQ 1 FCFWKTCF



L38 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:68700 HCAPLUS
DOCUMENT NUMBER: 100:68700
TITLE: Structure-activity relationships of highly potent and specific octapeptide analogs of somatostatin
AUTHOR(S): Bauer, Wilfried; Briner, Ulrich; Doepfner, Wolfgang; Haller, Roland; Huguenin, Rene; Marbach, Peter; Petcher, Trevor J.; Pless, Janos
CORPORATE SOURCE: Preclin. Res. Dep., Sandoz Ltd., Basel, CH-4002, Switz.
SOURCE: Pept., Proc. Eur. Pept. Symp., 17th (1983), Meeting Date 1982, 583-8. Editor(s): Blaha, Karel; Malon, Petr. de Gruyter: Berlin, Fed. Rep. Ger.
CODEN: 50GFAA
DOCUMENT TYPE: Conference

LANGUAGE: English

IT **88463-68-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and cyclization of)

RN 88463-68-7 HCAPLUS

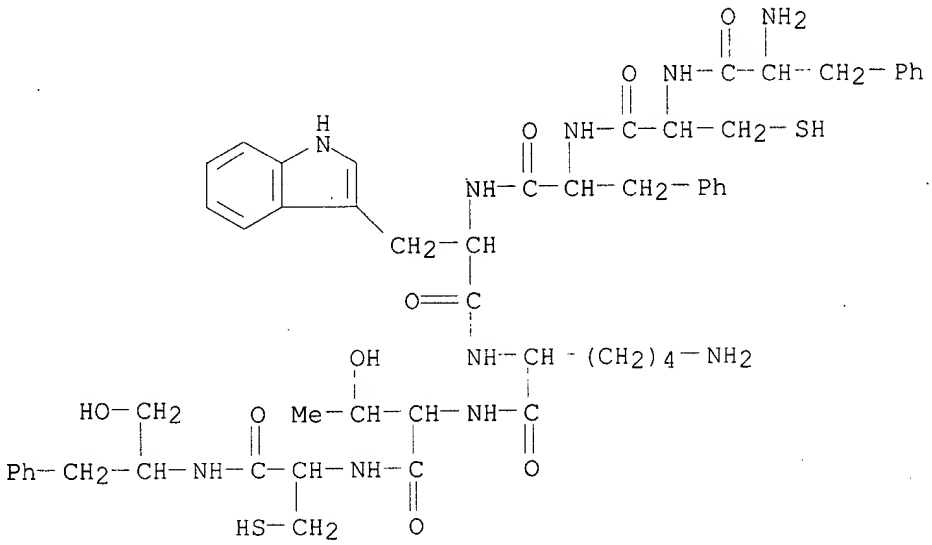
CN L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[1-(hydroxymethyl)-2-phenylethyl]-, (S)- (9CI) (CA INDEX NAME)

Poss.

NTE modified (modifications unspecified)

on end?

SEQ 1 FCFWKTCF



L38 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:23016 HCAPLUS
DOCUMENT NUMBER: 100:23016
TITLE: Polypeptides, their pharmaceutical compositions and their use
INVENTOR(S): Bauer, Wilfried; Pless, Janos
PATENT ASSIGNEE(S): Sandoz A.-G., Switz.
SOURCE: U.S., 10 pp. Cont.-in-part of U.S. Ser. No. 20
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 4395403 | A | 19830726 | US 1981-321663 | 19811116 |
| ZA 8007421 | A | 19820728 | ZA 1980-7421 | 19801127 |

PRIORITY APPLN. INFO.:
CH 1979-10524 19791127
CH 1980-4574 19800613
US 1980-208888 19801121

IT **79486-63-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 79486-63-8 HCAPLUS

CN L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[1-(hydroxymethyl)-2-phenylethyl]-, cyclic (2.fwdarw.7)-disulfide, (S)-, acetate (salt) (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 FCFWKTCF

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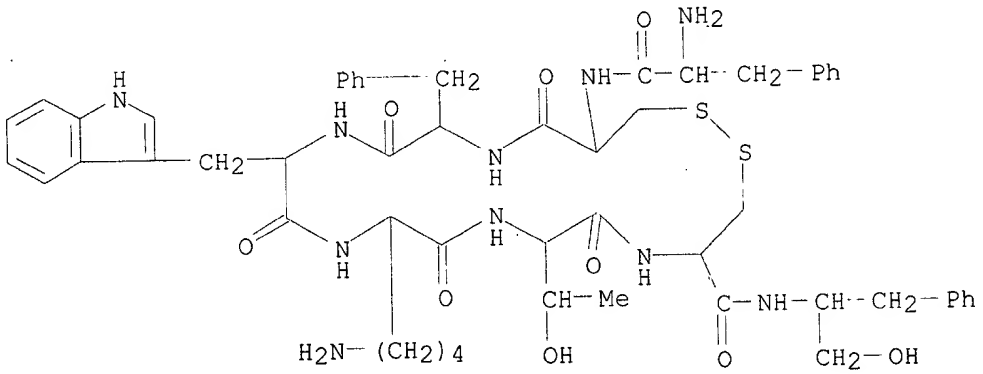
CRN 79486-62-7
CMF C54 H68 N10 O9 S2

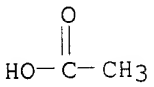
NTE modified (modifications unspecified)

SEQ 1 FCFWKTCF



CM 2

CRN 64-19-7
CMF C2 H4 O2



L38 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:4797 HCAPLUS
DOCUMENT NUMBER: 98:4797
TITLE: Polypeptides and their use as drugs
INVENTOR(S): Bauer, Wilfried; Pless, Janos
PATENT ASSIGNEE(S): Sandoz A.-G., Switz.
SOURCE: Belg., 27 pp.
CODEN: BEXXAL

DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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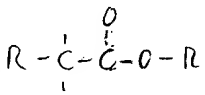
| BE 892315 | A1 | 19820901 | BE 1982-10440 | 19820301 |
| CH 647246 | A | 19850115 | CH 1981-1531 | 19810306 |
| DK 8200810 | A | 19820907 | DK 1982-810 | 19820224 |
| FI 8200689 | A | 19820907 | FI 1982-689 | 19820226 |
| FR 2501199 | A1 | 19820910 | FR 1982-3475 | 19820301 |
| FR 2501199 | B1 | 19860221 | | |
| DE 3207311 | A1 | 19821202 | DE 1982-3207311 | 19820301 |
| GB 2095261 | A | 19820929 | GB 1982-6136 | 19820302 |
| GB 2095261 | B2 | 19840815 | | |
| NL 8200828 | A | 19821001 | NL 1982-828 | 19820302 |
| US 4435385 | A | 19840306 | US 1982-353900 | 19820302 |
| SE 8201339 | A | 19820907 | SE 1982-1339 | 19820304 |
| CA 1188682 | A1 | 19850611 | CA 1982-397561 | 19820304 |
| IL 65167 | A1 | 19850630 | IL 1982-65167 | 19820304 |
| AU 8281164 | A1 | 19820909 | AU 1982-81164 | 19820305 |
| JP 57158745 | A2 | 19820930 | JP 1982-35698 | 19820305 |
| JP 03063559 | B4 | 19911001 | | |
| ES 510167 | A1 | 19831016 | ES 1982-510167 | 19820305 |
| ZA 8201491 | A | 19831026 | ZA 1982-1491 | 19820305 |
| HU 28423 | O | 19831228 | HU 1982-690 | 19820305 |
| ES 522916 | A1 | 19850301 | ES 1983-522916 | 19830601 |

PRIORITY APPLN. INFO.: CH 1981-1531 19810306
CH 1981-5723 19810904

IT **83795-90-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 83795-90-8 HCAPLUS
CN L-Phenylalanine, N-(1-oxotetradecyl)-D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-, methyl ester, cyclic (2.fwdarw.7)-disulfide, monoacetate (salt) (9CI) (CA INDEX NAME)

End



NTE modified (modifications unspecified)

SEQ 1 FCFWKTCF

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CRN 83795-89-5
CMF C69 H94 N10 O11 S2

NTE modified (modifications unspecified)

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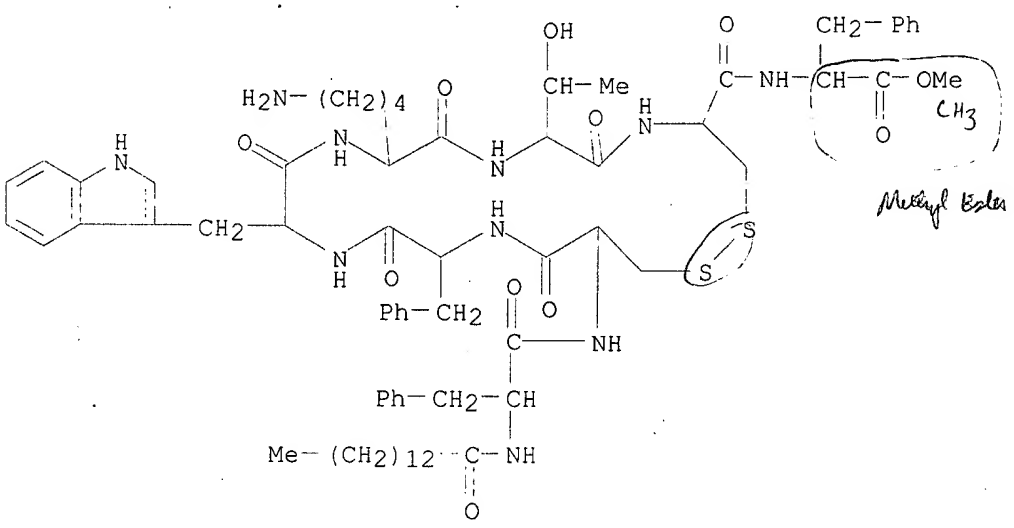
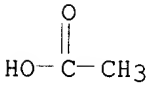


Mat Hizsida Eg 5-5

Methyl Ester

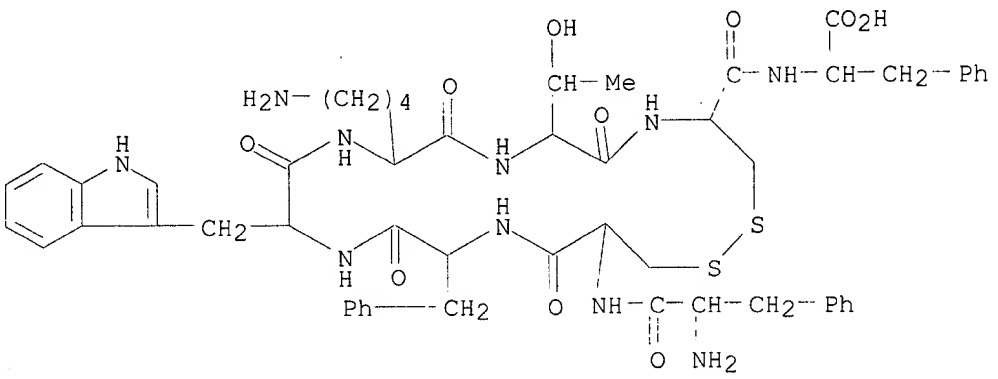
CM 2

CRN 64-19-7
CMF C2 H4 O2



L38 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:575266 HCAPLUS
DOCUMENT NUMBER: 97:175266
TITLE: SMS 201-995: a very potent and selective octapeptide analog of somatostatin with prolonged action
AUTHOR(S): Bauer, Wilfried; Briner, Ulrich; Doepfner, Wolfgang; Haller, Roland; Huguenin, Rene; Marbach, Peter; Petcher, Trevor J.; Pless, Janos
CORPORATE SOURCE: Preclin. Res., Sandoz Ltd., Basel, 4002, Switz.
SOURCE: Life Sciences (1982), 31(11), 1133-40
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **83214-21-5**
RL: BIOL (Biological study)
(somatostatin-like activity of, mol. structure in relation to)
RN 83214-21-5 HCAPLUS
CN L-Phenylalanine, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-, cyclic (2.fwdarw.7)-disulfide (9CI) (CA INDEX NAME)

SEQ 1 FCFWKTCF



L38 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:587679 HCAPLUS
DOCUMENT NUMBER: 95:187679
TITLE: Polypeptides, pharmaceutical compositions comprising said polypeptides and their use
INVENTOR(S): Bauer, Wilfried; Pless, Janos
PATENT ASSIGNEE(S): Sandoz A.-G., Switz.
SOURCE: Eur. Pat. Appl., 35 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 29579 | A1 | 19810603 | EP 1980-107181 | 19801119 |
| EP 29579 | B1 | 19830216 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| AT 2512 | E | 19830315 | AT 1980-107181 | 19801119 |
| FI 8003634 | A | 19810528 | FI 1980-3634 | 19801121 |
| FI 72981 | B | 19870430 | | |
| FI 72981 | C | 19870810 | | |
| DK 8005019 | A | 19810528 | DK 1980-5019 | 19801125 |
| DK 150146 | B | 19861215 | | |
| DK 150146 | C | 19870601 | | |
| AU 8064688 | A1 | 19810604 | AU 1980-64688 | 19801125 |
| AU 543198 | B2 | 19850404 | | |
| ES 497113 | A1 | 19821201 | ES 1980-497113 | 19801125 |
| HU 30257 | O | 19840328 | HU 1980-2817 | 19801125 |
| HU 185920 | B | 19850428 | | |
| CA 1182109 | A1 | 19850205 | CA 1980-365399 | 19801125 |
| IL 61561 | A1 | 19850228 | IL 1980-61561 | 19801125 |
| CS 228140 | P | 19840514 | CS 1980-8184 | 19801126 |
| JP 63051159 | B4 | 19881013 | JP 1980-167364 | 19801126 |
| JP 56090048 | A2 | 19810721 | | |
| ZA 8007421 | A | 19820728 | ZA 1980-7421 | 19801127 |
| ES 510751 | A1 | 19830416 | ES 1982-510751 | 19820324 |
| JP 63234000 | A2 | 19880929 | JP 1988-57316 | 19880308 |

PRIORITY APPLN. INFO.: CH 1979-10524 19791127
CH 1980-4574 19800613
EP 1980-107181 19801119

IT **79486-63-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 79486-63-8 HCAPLUS

CN L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[1-(hydroxymethyl)-2-phenylethyl]-, cyclic (2.fwdarw.7)-disulfide, (S)-, acetate (salt) (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 FCFWKTCF

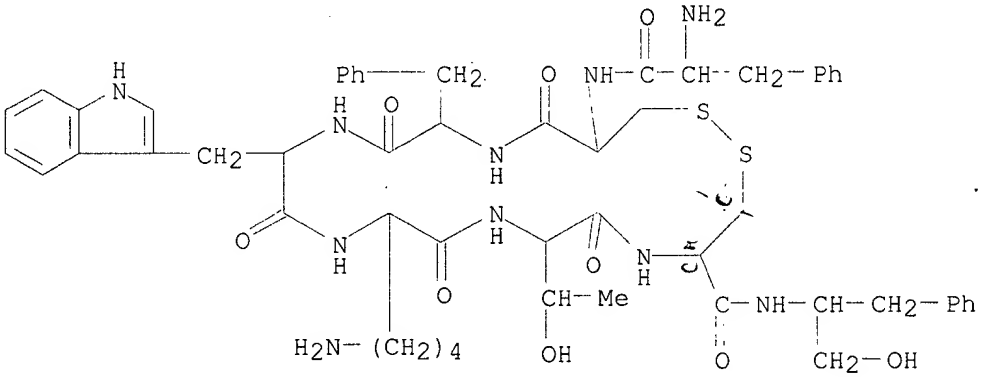
CL. 1 REJECT

CM 1

CRN 79486-62-7
CMF C54 H68 N10 O9 S2

NTE modified (modifications unspecified)

SEQ 1 FCFWKTCF



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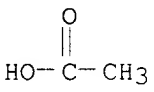
CMF C2 H4 O2



 Search of I. alone Then next indiv. Inventor Search

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=> fil hcaplus
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FILE COVERS 1907 - 20 Jun 2003  VOL 138 ISS 26
FILE LAST UPDATED: 19 Jun 2003  (20030619/ED)

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 substance identification.


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L1            17 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("HORNIK V"/AU OR "HORNIK
                 V"/IN OR "HORNIK VERED"/AU OR "HORNIK VERED"/IN)


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L1   ANSWER 1 OF 17  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:332670  HCAPLUS
DOCUMENT NUMBER:          136:341003
TITLE:                    Preparation of conformationally constrained backbone
                          cyclized somatostatin analogs
INVENTOR(S):              Hornik, Vered; Afargan, Michel M.;
                          Gellerman, Gary
PATENT ASSIGNEE(S):       Israel
SOURCE:                   U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of Appl.
                          No. PCT/IL99/00329.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   10
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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     US 2002052315      A1   20020502      US 2000-734583   20001213
     US 6051554         A    20000418      US 1998-100360   19980619
     US 6355613         B1   20020312      US 1998-203389   19981202
     WO 9965508         A1   19991223      WO 1999-IL329    19990615
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
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             JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
             MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
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TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

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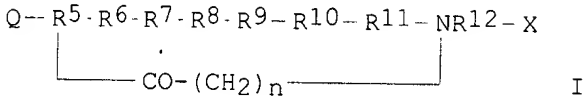
| US 1998-100360 | A2 | 19980619 |
| US 1998-203389 | A2 | 19981202 |
| WO 1999-IL329 | A2 | 19990615 |
| US 1995-488159 | A2 | 19950607 |
| US 1995-569042 | A2 | 19951207 |
| US 1996-690609 | A2 | 19960731 |

OTHER SOURCE(S): MARPAT 136:341003
GI



I

APPLIC.

AB Novel peptides, e.g., I [n = 1-5; X designates a terminal carboxy acid, amide or alc. group; Q is H or a mono- or disaccharide; R5 is .gamma.-aminobutyric acid, diaminobutyric acid, Gly, .beta.-Ala, 5-aminopentanoic acid, or aminohexanoic acid; R6 is D- or L-Phe or Tyr; R7 is D- or L-Trp, -Phe, -1-Nal (1-naphthalenealanine) or -2-Nal, or Tyr; R8 is D- or L-Trp; R9 is D- or L-Lys; R10 is Thr, Gly, Abu (2-aminobutanoic acid), Cys, Val, D- or L-Ala or -Phe; R11 is D- or L-Phe, -Ala, Nle, or Cys; R12 is Gly, Val, Leu, D- or L-Phe or 1Nal or 2Nal], are disclosed which are conformationally constrained backbone cyclized somatostatin analogs having somatostatin receptor sub-type selectivity. Thus, Phe(C3)-Cys*-Phe-D-Trp-Lys-Thr-Cys*-Phe-Phe(N3)-OH (PTR 3205), where one bridge connects the two building units (Phe-C3 and Phe N3, which are phenylalanine modified with carboxy or amine and a three carbon methylene spacer) and the second is a disulfide bridge formed between the two Cys residues, was prepd. by the solid-phase method and showed IC50 = 10-6 nM for inhibition of SRIF binding to transmembranal somatostatin receptors SST-R1, SST-R3 and SST-R5.

L1 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:182173 HCAPLUS
DOCUMENT NUMBER: 136:227293
TITLE: Selectivity of conformationally constrained backbone cyclized somatostatin analogs with respect to insulin, GH, and glucagon secretion and somatostatin receptor binding
INVENTOR(S): **Hornik, Vered**; Gellerman, Gary; Afargan, Mich El M.
PATENT ASSIGNEE(S): Peptor Limited, Israel
SOURCE: U.S., 21 pp., Cont.-in-part of U.S. 6,051,554.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6355613 | B1 | 20020312 | US 1998-203389 | 19981202 |
| US 6051554 | A | 20000418 | US 1998-100360 | 19980619 |
| CA 2335488 | AA | 19991223 | CA 1999-2335488 | 19990615 |
| WO 9965508 | A1 | 19991223 | WO 1999-IL329 | 19990615 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| AU 9942884 | A1 | 20000105 | AU 1999-42884 | 19990615 |
| AU 747515 | B2 | 20020516 | | |
| EP 1085896 | A1 | 20010328 | EP 1999-957020 | 19990615 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002518339 | T2 | 20020625 | JP 2000-554387 | 19990615 |
| US 2002052315 | A1 | 20020502 | US 2000-734583 | 20001213 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1996-690609 | A2 | 19960731 |
| US 1998-100360 | A2 | 19980619 |
| US 1995-488159 | A2 | 19950607 |
| US 1995-569042 | A2 | 19951207 |
| US 1998-203389 | A | 19981202 |
| WO 1999-IL329 | W | 19990615 |

OTHER SOURCE(S): MARPAT 136:227293

AB Novel peptides which are conformationally constrained backbone cyclized somatostatin analogs. Methods for synthesizing the somatostatin analogs and for producing libraries of the somatostatin analogs are also disclosed. Furthermore, pharmaceutical compns. comprising somatostatin analogs, and methods of using such compns. are disclosed.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:861504 HCAPLUS
DOCUMENT NUMBER: 134:25381
TITLE: Conformationally constrained backbone cyclized interleukin-6 antagonists, pharmaceutical compositions, and therapeutic use
INVENTOR(S): **Hornik, Vered**; Hadas, Eran
PATENT ASSIGNEE(S): Peptor Ltd., Israel
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000072864 | A1 | 20001207 | WO 2000-IL305 | 20000528 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1187624 | A1 | 20020320 | EP 2000-929763 | 20000528 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2003500453 | T2 | 20030107 | JP 2000-620973 | 20000528 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| IL 1999-130238 | A | 19990601 |

WO 2000-IL305 W 20000528
OTHER SOURCE(S): MARPAT 134:25381
AB Peptides are disclosed which are conformationally constrained backbone cyclized antagonists of IL-6. Methods for synthesizing the IL-6 antagonists are also disclosed. Furthermore, pharmaceutical compns. comprising IL-6 antagonists, and methods of using such compns. are disclosed.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:639186 HCAPLUS
DOCUMENT NUMBER: 133:238330
TITLE: Libraries of backbone-cyclized peptidomimetics
INVENTOR(S): Gilon, Chaim; **Hornik, Vered**
PATENT ASSIGNEE(S): Peptor Limited, Israel; Yissum Research Development Company of the Hebrew University In Jerusalem
SOURCE: U.S., 33 pp., Cont.-in-part of U.S. 5,723,575.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6117974 | A | 20000912 | US 1995-569042 | 19951207 |
| US 5723575 | A | 19980303 | US 1995-444135 | 19950518 |
| US 5770687 | A | 19980623 | US 1996-690090 | 19960731 |
| CA 2230861 | AA | 19970313 | CA 1996-2230861 | 19960828 |
| WO 9709344 | A2 | 19970313 | WO 1996-IL91 | 19960828 |
| WO 9709344 | A3 | 19970522 | | |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA | | | | |
| AU 9668361 | A1 | 19970327 | AU 1996-68361 | 19960828 |
| AU 714917 | B2 | 20000113 | | |
| JP 11500741 | T2 | 19990119 | JP 1996-511044 | 19960828 |
| EP 923601 | A2 | 19990623 | EP 1996-928663 | 19960828 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| US 6051554 | A | 20000418 | US 1998-100360 | 19980619 |

PRIORITY APPLN. INFO.:

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|---|---|---|
| IL 1991-99628 | A | 19911002 |
| US 1992-955380 | B2 | 19921001 |
| US 1995-444135 | A2 | 19950518 |
| IL 1995-115096 | A | 19950829 |
| US 1995-488159 | A2 | 19950607 |
| US 1995-569042 | A2 | 19951207 |
| US 1996-690609 | A2 | 19960731 |
| WO 1996-IL91 | W | 19960828 |

OTHER SOURCE(S): MARPAT 133:238330
AB Libraries of novel backbone-cyclized peptide analogs are formed by means of bridging groups attached via the alpha nitrogens of amino acid derivs. to provide novel non-peptidic linkages. Novel building units used in the synthesis of these backbone-cyclized peptide analogs are N-functionalized amino acids constructed to include a spacer and a terminal functional group. One or more of these N-functionalized amino acids are incorporated into a library of peptide sequences, preferably during solid phase peptide synthesis. The reactive terminal functional groups are protected by

specific protecting groups that can be selectively removed to effect either backbone-to-backbone or backbone-to-side chain cyclizations. The invention is exemplified by libraries of backbone-cyclized bradykinin analogs, somatostatin analogs, BPI analogs and Substance P analogs having biol. activity. Further embodiments of the invention are Interleukin-6 receptor derived peptides having ring structures involving backbone cyclization.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:253013 HCAPLUS
DOCUMENT NUMBER: 132:289222
TITLE: Conformationally constrained backbone cyclized somatostatin analogs
INVENTOR(S): **Hornik, Vered**; Gellerman, Gary; Afargan, Mich El M.
PATENT ASSIGNEE(S): Peptor Limited, Israel
SOURCE: U.S., 18 pp., Cont.-in-part of U.S. 5,748,643.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| US 6051554 | A | 20000418 | US 1998-100360 | 19980619 |
| US 5811392 | A | 19980922 | US 1995-488159 | 19950607 |
| US 6117974 | A | 20000912 | US 1995-569042 | 19951207 |
| US 6265375 | B1 | 20010724 | US 1998-120237 | 19980722 |
| US 6355613 | B1 | 20020312 | US 1998-203389 | 19981202 |
| CA 2335488 | AA | 19991223 | CA 1999-2335488 | 19990615 |
| WO 9965508 | A1 | 19991223 | WO 1999-IL329 | 19990615 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9942884 | A1 | 20000105 | AU 1999-42884 | 19990615 |
| AU 747515 | B2 | 20020516 | | |
| EP 1085896 | A1 | 20010328 | EP 1999-957020 | 19990615 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002518339 | T2 | 20020625 | JP 2000-554387 | 19990615 |
| US 6407059 | B1 | 20020618 | US 2000-580905 | 20000531 |
| US 2002052315 | A1 | 20020502 | US 2000-734583 | 20001213 |

PRIORITY APPLN. INFO.:

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| US 1995-488159 | A2 | 19950607 |
| US 1995-569042 | A2 | 19951207 |
| US 1996-690609 | A2 | 19960731 |
| IL 1991-99628 | A | 19911002 |
| US 1992-955380 | B2 | 19921001 |
| IL 1994-109943 | A | 19940608 |
| US 1995-444135 | A2 | 19950518 |
| IL 1995-115096 | A | 19950829 |
| US 1998-100360 | A2 | 19980619 |
| US 1998-120237 | A3 | 19980722 |
| US 1998-203389 | A | 19981202 |
| WO 1999-IL329 | W | 19990615 |

OTHER SOURCE(S): MARPAT 132:289222

AB According to the present invention, novel peptidomimetic compds., which are characterized in that they incorporate novel building units with bridging groups attached to the alpha nitrogens of alpha amino acids, have now been generated. Specifically, these compds. are backbone cyclized somatostatin analogs comprising a peptide sequence of four to twelve amino acids that incorporates at least two building units, each of which contains one nitrogen atom of the peptide backbone connected to a bridging group comprising an amide, thioether, thioester or disulfide, wherein the at least two building units are connected to the bridging group to form a cyclic structure. Preferably, the peptide sequence incorporates five to eight amino acids. The cyclic somatostatin analogs are resistant to biodegrdn. The selectivity of the analogs with respect to GH, insulin and glucagon and with respect to somatostatin receptors is shown. Methods for synthesizing the somatostatin analogs and for producing libraries of the somatostatin analogs are also disclosed. Furthermore, pharmaceutical compns. comprising somatostatin analogs, and methods of using such compns. are disclosed.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:811096 HCAPLUS
DOCUMENT NUMBER: 132:50250
TITLE: Preparation of conformationally constrained backbone cyclized somatostatin analogs
INVENTOR(S): **Hornik, Vered**; Afargan, Michel M.; Gellerman, Gary
PATENT ASSIGNEE(S): Peptor Ltd., Israel
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 9965508 | A1 | 19991223 | WO 1999-IL329 | 19990615 |
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| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6051554 | A | 20000418 | US 1998-100360 | 19980619 |
| US 6355613 | B1 | 20020312 | US 1998-203389 | 19981202 |
| CA 2335488 | AA | 19991223 | CA 1999-2335488 | 19990615 |
| AU 9942884 | A1 | 20000105 | AU 1999-42884 | 19990615 |
| AU 747515 | B2 | 20020516 | | |
| EP 1085896 | A1 | 20010328 | EP 1999-957020 | 19990615 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002518339 | T2 | 20020625 | JP 2000-554387 | 19990615 |
| US 2002052315 | A1 | 20020502 | US 2000-734583 | 20001213 |

PRIORITY APPLN. INFO.:
US 1998-100360 A 19980619
US 1998-203389 A 19981202
US 1995-488159 A2 19950607
US 1995-569042 A2 19951207
US 1996-690609 A2 19960731

OTHER SOURCE(S): MARPAT 132:50250 WO 1999-IL329 W 19990615
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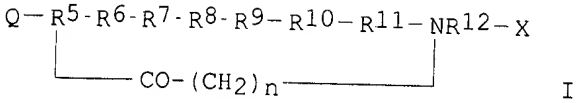


I

AB Novel peptides, e.g., I [n = 1-5; X designates a terminal carboxy acid, amide or alc. group; Q is H or a mono- or disaccharide; R5 is .gamma.-aminobutyric acid, diaminobutyric acid, Gly, .beta.-Ala, 5-aminopentanoic acid, or aminohexanoic acid; R6 is D- or L-Phe or Tyr; R7 is D- or L-Trp, -Phe, -1-Nal (1-naphthalenealanine) or -2-Nal, or Tyr; R8 is D- or L-Trp; R9 is D- or L-Lys; R10 is Thr, Gly, Abu (2-aminobutanoic acid), Cys, Val, D- or L-Ala or -Phe; R11 is D- or L-Phe, -Ala, Nle, or Cys; R12 is Gly, Val, Leu, D- or L-Phe or 1Nal or 2Nal], are disclosed which are conformationally constrained backbone cyclized somatostatin analogs having somatostatin receptor sub-type selectivity. Thus, Phe(C3)-Cys*-Phe-D-Trp-Lys-Thr-Cys*-Phe-Phe(N3)-OH (PTR 3205), where one bridge connects the two building units (Phe-C3 and Phe N3, which are phenylalanine modified with carboxy or amine and a three carbon methylene spacer) and the second is a disulfide bridge formed between the two Cys residues, was prepd. by the solid-phase method and showed IC50 = 10-6 nM for inhibition of SRIF binding to transmembranal somatostatin receptors SST-R1, SST-R3 and SST-R5.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:597740 HCAPLUS
DOCUMENT NUMBER: 129:343696
TITLE: Cycloscan: backbone cyclic conformationally constraint libraries of peptides
AUTHOR(S): Gilon, C.; Muller, D.; Bitan, G.; Salitra, Y.; Goldwasser, I.; **Hornik, V.**
CORPORATE SOURCE: Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SOURCE: Peptides 1996, Proceedings of the European Peptide Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (1998), Meeting Date 1996, 423-424. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK.
CODEN: 66RCA5
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report on the prepn., characterization, and biol. screening of backbone cyclic libraries comprising a collection of different conformations of the screened peptide. The method is illustrated with and active analog of somatostatin.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:427795 HCAPLUS
DOCUMENT NUMBER: 129:95723
TITLE: Preparation of conformationally constrained backbone cyclized somatostatin analogs and combinatorial libraries
INVENTOR(S): **Hornik, Vered**; Seri-Levy, Alon; Gellerman,

Use instead of

PATENT ASSIGNEE(S): Gary; Gilon, Chaim
Peptor Ltd., Israel; Yissim Research Development Co. of Hebrew University of Jerusalem

SOURCE: U.S., 35 pp., Cont.-in-part of U.S. Ser. No. 488,159.
CODEN: USXXAM

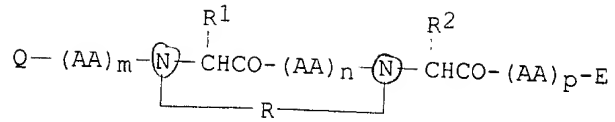
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DB Patt. US 5770687 | A | 19980623 | US 1996-690090 | 19960731 |
| US 5811392 | A | 19980922 | US 1995-488159 | 19950607 |
| US 6117974 | A | 20000912 | US 1995-569042 | 19951207 |
| WO 9804583 | A1 | 19980205 | WO 1997-IL261 | 19970730 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9736331 | A1 | 19980220 | AU 1997-36331 | 19970730 |
| AU 711100 | B2 | 19991007 | | |
| EP 920446 | A1 | 19990609 | EP 1997-932978 | 19970730 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| CN 1231672 | A | 19991013 | CN 1997-198197 | 19970730 |
| BR 9710636 | A | 20000111 | BR 1997-10636 | 19970730 |
| JP 2000516592 | T2 | 20001212 | JP 1998-508666 | 19970730 |
| US 6265375 | B1 | 20010724 | US 1998-120237 | 19980722 |
| KR 2000029654 | A | 20000525 | KR 1999-700727 | 19990129 |
| US 6407059 | B1 | 20020618 | US 2000-580905 | 20000531 |

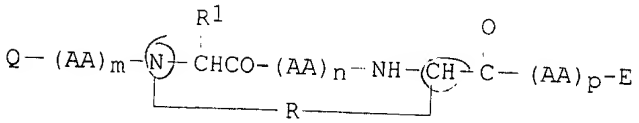
PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1995-488159 | A2 | 19950607 |
| US 1995-569042 | A2 | 19951207 |
| IL 1991-99628 | A | 19911002 |
| US 1992-955380 | B2 | 19921001 |
| IL 1994-109943 | A | 19940608 |
| US 1995-444135 | A2 | 19950518 |
| IL 1995-115096 | A | 19950829 |
| US 1996-690090 | A | 19960731 |
| WO 1997-IL261 | W | 19970730 |
| US 1998-120237 | A3 | 19980722 |

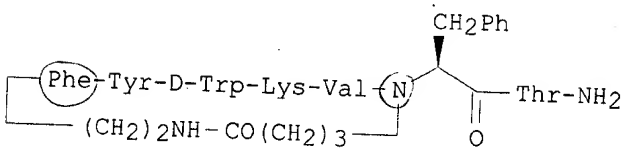
OTHER SOURCE(S): MARPAT 129:95723
GI



I



II



III

APPL. Teach all 3 species of cl. 1

AB The novel conformationally constrained backbone cyclized somatostatin analogs I and II [m, n, p = independently 0-8; AA = amino acid residue wherein each amino acid residue may be the same or different; Q = H, acyl group; E = OH, carboxyl protective group, amino group, or the terminal carboxy group can be reduced to CH2OH; R1, R2 = independently optionally protected amino acid side chain; R = X-M-Y-W-Z, X-M-Z; M, W = independently amide, thioether, thioester, disulfide; X, Y, Z = independently alkylene, substituted alkylene, arylene, homo- or heterocycloarylene, substituted cycloalkylene] and combinatorial libraries thereof are disclosed. Methods for synthesizing the somatostatin analogs and for producing the libraries of the somatostatin analogs are also disclosed. Furthermore, pharmaceutical compns. comprising somatostatin analogs, and methods of using such compns. in the treatment of endocrine disorders, neoplasms and metabolic disorders are also disclosed. Thus, cyclopeptide III (PTR 3046) was prepd. by solid-phase methods on a Rink amide resin using 9-fluorenylmethoxycarbonyl (Fmoc) backbone protection and allyl protection for the cyclic amide residues. PTR 3046 and related cyclopeptides and combinatorial libraries were tested in vitro for binding to a variety of different somatostatin receptors in Chinese hamster ovary cells expressing the various receptors.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:119596 HCAPLUS

DOCUMENT NUMBER: 128:226364

TITLE: A Backbone-Cyclic, Receptor 5-Selective Somatostatin Analog: Synthesis, Bioactivity, and Nuclear Magnetic Resonance Conformational Analysis

AUTHOR(S): Gilon, Chaim; Huenges, Martin; Mathae, Barbara; Gellerman, Gary; **Hornik, Vered**; Afargan, Michel; Amitay, Oved; Ziv, Ofer; Feller, Etty; Gamliel, Asher; Shohat, Dvira; Wanger, Mazal; Arad, Oded; Kessler, Horst

CORPORATE SOURCE: Department of Organic Chemistry, Hebrew University, Jerusalem, Israel

SOURCE: Journal of Medicinal Chemistry (1998), 41(6), 919-929

No — Date No Good

PUBLISHER: CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: American Chemical Society
LANGUAGE: Journal
English

AB Cyclo(PheN2-Tyr-D-Trp-Lys-Val-PheC3)-Thr-NH2 (PTR 3046), a backbone-cyclic somatostatin analog was synthesized by solid-phase methodol. The binding characteristics of PTR 3046 to the different somatostatin receptors, expressed in CHO cells, indicate high selectivity to the SSTR5 receptor. PTR 3046 is highly stable against enzymic degrdn. as detd. in vitro by incubation with rat renal homogenate and human serum. The biol. activity of PTR 3046 in vivo was detd. in rats. PTR 3046 inhibits bombesin- and caerulein-induced amylase and lipase release from the pancreas without inhibiting growth hormone or glucagon release. The major conformation of PTR 3046 in CD3OH, as detd. by NMR, is defined by a type II' .beta.-turn at D-Trp-Lys and a cis amide bond at Val-PheC3.

L1 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:102893 HCAPLUS
DOCUMENT NUMBER: 128:180672
TITLE: Conformationally constrained backbone cyclized somatostatin analogs
INVENTOR(S): **Hornik, Vered**; Seri-Levy, Alon; Gellerman, Gary; Gilon, Chaim
PATENT ASSIGNEE(S): Peptor Ltd., Israel; Yissum Research Development Company of the Hebrew; Hornik, Vered; Seri-Levy, Alon; Gellerman, Gary; Gilon, Chaim
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9804583 | A1 | 19980205 | WO 1997-IL261 | 19970730 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5770687 | A | 19980623 | US 1996-690090 | 19960731 |
| AU 9736331 | A1 | 19980220 | AU 1997-36331 | 19970730 |
| AU 711100 | B2 | 19991007 | | |
| EP 920446 | A1 | 19990609 | EP 1997-932978 | 19970730 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| BR 9710636 | A | 20000111 | BR 1997-10636 | 19970730 |
| JP 2000516592 | T2 | 20001212 | JP 1998-508666 | 19970730 |

PRIORITY APPLN. INFO.:
US 1996-690090 A 19960731
US 1995-488159 A2 19950607
US 1995-569042 A2 19951207
WO 1997-IL261 W 19970730

OTHER SOURCE(S): MARPAT 128:180672

AB Methods for synthesizing cyclized somatostatin analogs Q-(AA)a-NR-CHR1-CO-(AA)b-NR-CHR2-CO-(AA)c-E(R2 = a bond, a-c are 0-8, AA is an amino acid residue, Q = H, acyl, E = OH, carboxy-protecting group, or amino group, or the terminal carboxyl group can be reduced to CH2OH) and for producing libraries of the somatostatin analogs are disclosed. Thus, SST-Gly6,Gly11 analogs bridged at positions 1-3 were prepd. manually

or with an automatic peptide synthesizer. Physiol. examples are given.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:296920 HCAPLUS
DOCUMENT NUMBER: 126:277779
TITLE: Libraries of backbone-cyclized peptidomimetics
INVENTOR(S): **Hornik, Vered**; Gilon, Chaim
PATENT ASSIGNEE(S): Peptor Limited, Israel; Yissum Research Development Company of the Hebrew University; Hornik, Vered; Gilon, Chaim
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9709344 | A2 | 19970313 | WO 1996-IL91 | 19960828 |
| WO 9709344 | A3 | 19970522 | | |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA | | | | |
| US 6117974 | A | 20000912 | US 1995-569042 | 19951207 |
| AU 9668361 | A1 | 19970327 | AU 1996-68361 | 19960828 |
| AU 714917 | B2 | 20000113 | | |
| JP 11500741 | T2 | 19990119 | JP 1996-511044 | 19960828 |
| EP 923601 | A2 | 19990623 | EP 1996-928663 | 19960828 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| IL 1995-115096 | A | 19950829 |
| US 1995-569042 | A | 19951207 |
| IL 1991-99628 | A | 19911002 |
| US 1992-955380 | B2 | 19921001 |
| US 1995-444135 | A2 | 19950518 |
| WO 1996-IL91 | W | 19960828 |

OTHER SOURCE(S): MARPAT 126:277779

AB Libraries of novel backbone-cyclized peptide analogs are formed by means of bridging groups attached via the alpha nitrogens of amino acid derivs. to provide novel non-peptidic linkages. Novel building units used in the synthesis of these backbone-cyclized peptide analogs are N.alpha. (.omega.-functionalized) amino acids constructed to include a spacer and a terminal functional group. One or more of these N.alpha. (.omega.-functionalized) amino acids are incorporated into a library of peptide sequences, preferably during solid phase peptide synthesis. The reactive terminal functional groups are protected by specific protecting groups that can be selectively removed to effect either backbone-to-backbone or backbone-to-side chain cyclizations. The invention is exemplified by libraries of backbone-cyclized bradykinin analogs, somatostatin analogs, BPI analogs and Substance P analogs having biol. activity. Further embodiments of the invention are Interleukin-6 receptor derived peptides having ring structures involving backbone cyclization.

L1 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:219531 HCAPLUS

✓ Audeud
✓ Rec'd

TITLE: Backbone-cyclic peptides in peptide drug discovery?
AUTHOR(S): Arad, O.; Afargan, M.; Diskin, Y.; Feller, E.; Gamliel, A.; Gellerman, G.; Goldwasser, I.; Hadas, E.; **Hornik, V.**; et al.
CORPORATE SOURCE: Peptor Ltd., Rehovot, 76326, Israel
SOURCE: Book of Abstracts, 211th ACS National Meeting, New Orleans, LA, March 24-28 (1996), I&EC-012. American Chemical Society: Washington, D. C.
CODEN: 62PIAJ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

Include Not enabled

AB Backbone-cyclization of peptides is accomplished via a bridge between two backbone amide nitrogens (C. Gilon, D. Halle, M. Chorev, Z. Selinger and G. Byk, Biopolymers 1991, 31, 745). Backbone-cyclization can be carried out between any two residues in the sequence without altering the side chains of the amino acid residues involved in the cyclization. These side chains may be important for the biol. activity of the peptide. We have recently synthesized backbone-cyclic peptides corresponding to the Somatostain family and to Bactericidal Permeability Increasing Protein. Comparisons of the bioactivity of cyclic and non-cyclic structures indicate the effect that cyclization has on activity. In particular, a significant increase in biostability and in selectivity is seen upon cyclization. By employing the backbone-cyclization method, series of conformationally constrained peptides can be prepd. in which the sequence is identical and the peptides differ in the cyclization points and in the size and structure of the cyclization bridge (Cycloscan). We are studying the structure of these conformationally constrained peptides by computer modeling.

L1 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:541399 HCAPLUS
DOCUMENT NUMBER: 122:286086
TITLE: Preparation and screening of highly diverse peptide libraries for binding activity
INVENTOR(S): Hadas, Eran; **Hornik, Vered**
PATENT ASSIGNEE(S): Interpharm Laboratories Ltd., Israel
SOURCE: Eur. Pat. Appl., 63 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 639584 | A1 | 19950222 | EP 1994-109577 | 19940621 |
| EP 639584 | B1 | 19980401 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| CA 2126359 | AA | 19941223 | CA 1994-2126359 | 19940621 |
| AT 164591 | E | 19980415 | AT 1994-109577 | 19940621 |
| ES 2114633 | T3 | 19980601 | ES 1994-109577 | 19940621 |
| AU 9464873 | A1 | 19950105 | AU 1994-64873 | 19940622 |
| AU 678460 | B2 | 19970529 | | |
| ZA 9404474 | A | 19950214 | ZA 1994-4474 | 19940622 |
| JP 07194382 | A2 | 19950801 | JP 1994-164756 | 19940622 |

PRIORITY APPLN. INFO.: IL 1993-106106 19930622

AB A method for the prepn. of high-d. peptide (or other polymer) libraries, and for screening such libraries for mols. having the capacity to recognize targets of choice, is provided. The peptide library is synthesized on beads, but instead of a single peptide sequence, a single family of related peptide sequences are synthesized on each bead. The peptide library, in turn, includes many different families of peptides, with each family being found on one or more beads. Because the peptide

library is arranged so that the peptide complement of each bead is constrained, the library is said to be structured. This structured library is then subjected to a round of screening. If a bead is marked by an affinity reagent, it indicates that one or more of the peptides in its family are bound by the affinity reagent. The peptide mixt. on the bead is then sequenced to det. the common N-terminal portion, the familial marker. In the next round of screening, a sublibrary of the library of the prior round is constructed, in which all peptides possess the familial marker of the successful family in the last library. Each bead of this new library carries only peptides belonging to a subfamily of the aforementioned family. When this sublibrary is screened with an affinity reagent, the beads which are bound are those whose subfamilies include a binding peptide. The process is then repeated, with each successful family of the library of one screening round becoming, in the next round, a new library, which in turn is divided into families. Eventually, the entire sequence of the binding peptide is known. The method is illustrated by (1) the synthesis of a peptide library from 37 different amino acids on Eupergit C beads or aminomethylated polystyrene/divinylbenzene and screening with rhodamine-labeled TBP1 (tumor necrosis factor binding protein p55), (2) model straining of a heptapeptide library with monoclonal antibody to human .beta.-endorphin, and (3) a library prepd. from 74 amino acids on glass beads and screened with TBP1. Theor., this method increases the delivery of the library by as much as 7 orders of magnitude, i.e., to as many as 1015 different peptide sequences.

L1 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:678197 HCAPLUS
DOCUMENT NUMBER: 121:278197
TITLE: Variations in effectivity of mechanisms which restrict the cellular response to TNF
AUTHOR(S): Wallach, D.; Bigda, J.; Brakebusch, C.; Beletsky, I.; Aderka, D.; Holtmann, H.; Englemann, H.; **Hornik, V.**; Shemer, Y.; et al.
CORPORATE SOURCE: Department Membrane Research and Biophysics, Weizmann Institute Science, Rehovot, 76100, Israel
SOURCE: Challenges of Modern Medicine (1994), 3(MOLECULAR BASIS OF INFLAMMATION), 169-78
CODEN: CHMME3
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 31 refs., discussing how the variation in the relative expression of 2 TNF receptor species affect the extent of desensitization to the cytocidal effect of TNF, how signaling by TNF receptors and formation of the sol. forms are mechanistically distinct, and how variations in the effectivity of mechanisms which restrict the activity of TNF may be genetically defined.

L1 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:477731 HCAPLUS
DOCUMENT NUMBER: 121:77731
TITLE: Self-encoded, highly condensed solid phase-supported peptide library for identification of ligand-specific peptides
AUTHOR(S): **Hornik, Vered**; Hadas, Eran
CORPORATE SOURCE: Department of Molecular Genetics and Virology, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Reactive Polymers (1994), 22(3), 213-20
CODEN: REPLEN; ISSN: 0923-1137
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The diversity of peptide libraries synthesized according to the "mixing and portioning" concept producing libraries contg. one peptide per bead is

limited by the no. of beads. A method for the generation and screening of peptide libraries with increased mol. diversity by synthesis of many peptides on each of the beads is described. According to this approach, in each synthesis cycle, every portion of the beads gets a mixt. of amino acids, thus the total no. of peptides is larger than the no. of beads in the library. The degree of heterogeneity increases from the N- to the C-terminus. Positions close to the N-terminus include relatively few amino acids, whereas positions closer to the C-terminus include a higher no. of amino acids. This structure allows generation of extensive diversity on each bead, while still retaining the ability to identify the peptide by N-terminal sequencing. The identification of the peptides on selected beads is achieved by sequencing and by using a self-encoding system. This self-encoding system allows the use of coded as well as non-coded amino acids which cannot be identified by automatic sequencers. According to this system, each non-coded amino acid is presented in a mixt. with a coded amino acid. The coded amino acid serves as an indicator for the presence of the non-coded one. Only a portion of the target sequence is identified by N-terminal sequencing. Once partial sequence information is obtained, secondary libraries are synthesized in order to find out which amino acids present in each position are responsible for binding a ligand. The new approach enables generation and screening of up to about 1015 peptides per library, increasing the diversity of solid phase-screened peptides, or other non-sequenceable polymer libraries, by up to 107-fold, thereby increasing the chances of discovering structures of interest.

L1 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:548989 HCAPLUS
DOCUMENT NUMBER: 117:148989
TITLE: Variation in serum levels of the soluble TNF receptors among healthy individuals
AUTHOR(S): Aderka, Dan; Engelmann, Hartmut; Shemer-Avni, Yonath; **Hornik, Vered**; Galil, Aaron; Sarov, Batia; Wallach, David
CORPORATE SOURCE: Dep. Med., "T." Ichilov Hosp., Tel Aviv-Jaffa, 64239, Israel
SOURCE: Lymphokine and Cytokine Research (1992), 11(3), 157-9
CODEN: LCREEY; ISSN: 1056-5477
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sol. forms of the two receptors for tumor necrosis factor (TNF) are present in human sera at concns. that increase greatly in various disease states as well as varying among healthy individuals. Measurements of the sol. TNF receptor (sTNF-R) concns. in healthy individuals at time lapses of 3 mo (17 individuals) or 1 yr (51 individuals) showed a significant correlation between the first and the second measurements from each individual, implying that individual differences are stable. Since the sTNF-Rs are believed to function as physiol. attenuators of TNF activity, these steady individual differences may contribute to differences in the severity of harmful effects of TNF in disease states.

L1 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:446021 HCAPLUS
DOCUMENT NUMBER: 117:46021
TITLE: Soluble and cell surface receptors for tumor necrosis factor
AUTHOR(S): Wallach, D.; Engelmann, H.; Nophar, Y.; Aderka, D.; Kemper, O.; **Hornik, V.**; Holtmann, H.; Brakebusch, C.
CORPORATE SOURCE: Dep. Mol. Genet. Virol., Weizmann Inst. Sci., Rehovot, 76100, Israel
SOURCE: Agents and Actions Supplements (1991), 35(Prog. Inflammation Res. Ther.), 51-7

CODEN: AASUDJ; ISSN: 0379-0363
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 31 refs. Tumor necrosis factor (TNF) initiates its multiple effects on cell function by binding at a high affinity to specific cell surface receptors. Two different mol. species of these receptors, which are expressed differentially in different cells, have been identified. The cDNAs of both receptors have recently been cloned. The intracellular domains of the two receptors differ in structure, suggesting that they mediate different activities. Their extracellular domains, however, are structurally related. Both contain cysteine-rich repeats which are homologous to repeated structures found in the extracellular domains of the nerve growth factor receptor and the CDw40 protein. Truncated sol. forms of the two receptors, corresponding to these cysteine-rich repeated structures, have been detected in human urine and were later found to be present also in the serum. The serum levels of those sol. TNF receptors increase dramatically in certain pathol. situations. Release of the sol. receptors from the cells seems to occur by proteolytic cleavage of the cell surface forms and appears to be a way of down-regulating the cell response to TNF. Because of their ability to bind TNF, the sol. receptors exert an inhibitory effect on TNF function, and may thus act as physiol. attenuators of its activity.

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L1 17 SEA FILE=HCAPLUS ABB=ON PLU=ON ("HORNIK V"/AU OR "HORNIK V"/IN OR "HORNIK VERED"/AU OR "HORNIK VERED"/IN)
L2 9 SEA FILE=HCAPLUS ABB=ON PLU=ON ("AFARGAN M"/AU OR "AFARGAN M"/IN OR "AFARGAN MICH EL M"/AU OR "AFARGAN MICH EL M"/IN OR "AFARGAN MICHAEL"/AU OR "AFARGAN MICHEL"/AU OR "AFARGAN MICHEL M"/AU OR "AFARGAN MICHEL M"/IN OR "AFARGAN MISHEL"/AU) NOT L1

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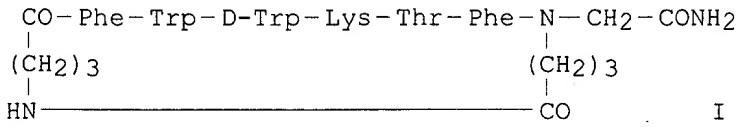
L2 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:425744 HCAPLUS
TITLE: Synthesis of novel protected N.alpha.(o-thioalkyl) amino acid building units and their incorporation into backbone cyclic disulfide bridged peptides
AUTHOR(S): Gazal, Sharon; Gellerman, Gary; Karpov, Olga; Litman, Pninit; Bracha, Moshe; **Afargan,. Michel**; Gilon, Chaim
CORPORATE SOURCE: Department of Organic Chemistry, Hebrew University, Jerusalem, 91904, Israel
SOURCE: Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries: Peptides, Proteins and Nucleic Acids--Small Molecule Organic Chemistry Diversity, Collected Papers, International Symposium, 7th, Southampton, United Kingdom, Sept. 18-22, 2001 (2002), Meeting Date 2001, 189-191. Editor(s): Epton, Roger. Mayflower Worldwide Ltd.: Kingswinford, UK. CODEN: 69DYT7; ISBN: 0-9515735-4-3
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Unavailable
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:692513 HCAPLUS
DOCUMENT NUMBER: 138:117735
TITLE: Human somatostatin receptor specificity of backbone-cyclic analogs containing novel sulfur building units
AUTHOR(S): Gazal, Sharon; Gellerman, Gary; Ziv, Ofer; Karpov, Olga; Litman, Pninit; Bracha, Moshe; **Afargan, Michel**; Gilon, Chaim
CORPORATE SOURCE: Department of Organic Chemistry, Hebrew University, Jerusalem, 91904, Israel
SOURCE: Peptides: The Wave of the Future, Proceedings of the Second International and the Seventeenth American Peptide Symposium, San Diego, CA, United States, June 9-14, 2001 (2001), 626-627. Editor(s): Lebl, Michal; Houghten, Richard A. American Peptide Society: San Diego, Calif.
CODEN: 69DBAL; ISBN: 0-9715560-0-8
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The synthesis and the biol. properties of novel disulfide bridged backbone cyclic somatostatin analogs were examd. These analogs were prepd. to investigate the influence of the ring size and ring chem. on the binding profile of a parent analog named PTR 3173. PTR 3173 is 1000-fold more potent in the in vivo inhibition of growth hormone (GH) than of glucagon and 10,000-fold more potent inhibitor of GH than of insulin release. This pharmacol. property is ascribed to the unique binding profile of PTR 3173 and it was suggested that the binding to a specific combination of somatostatin receptors and not a single receptor dets. the physiol. properties of the SST analog. Studies of binding of PTP 73 disulfide-bridged, backbone cyclic analogs to SSTR receptors suggest the effect of ring chem., ring size, and ring position of the peptide template on receptor binding selectivity. The disulfide analogs of PTR 3173 were also highly resistant to a broad spectrum of proteolytic activity compared to somatostatin that was degraded within a few minutes.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:197431 HCAPLUS
DOCUMENT NUMBER: 136:386384
TITLE: Human Somatostatin Receptor Specificity of Backbone-Cyclic Analogues Containing Novel Sulfur Building Units
AUTHOR(S): Gazal, Sharon; Gelerman, Garry; Ziv, Ofer; Karpov, Olga; Litman, Pninit; Bracha, Moshe; **Afargan, Michel**; Gilon, Chaim
CORPORATE SOURCE: Department of Organic Chemistry, Hebrew University, Jerusalem, 91904, Israel
SOURCE: Journal of Medicinal Chemistry (2002), 45(8), 1665-1671
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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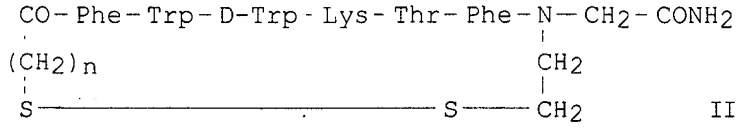
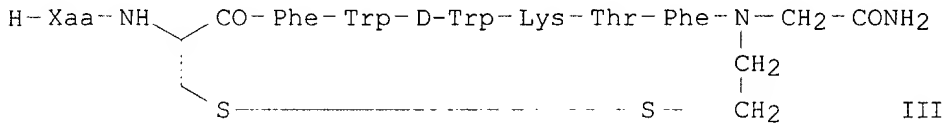
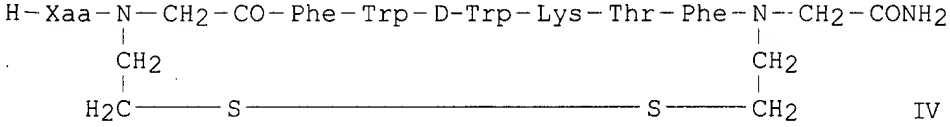


II



III



IV

AB Somatostatin-14 (somatostatin) and its clin. available analogs (octreotide, lanreotide and vapreotide) are potent inhibitors of growth hormone, insulin, and glucagon release. Recently, the synthesis of PTR-3173 (I), a novel cyclic somatostatin analog with in vivo endocrine selectivity, was described. I exhibited high affinity to human recombinant somatostatin receptors (hsst) hsst2, hsst4 and hsst5. Its novel binding profile included potent in vivo inhibition of growth hormone but not of insulin release. Here, the synthesis, bioactivity, and structure-activity relationship studies of peptides II (n = 1, 2), III (Xaa = nil, D-Phe) and IV (Xaa = nil, D-Phe, D-Nal) are reported and compared to those of I. In II-IV, the lactam bridge of I was replaced by a backbone disulfide bridge. II-IV showed significant metabolic stability as tested in various enzyme mixts. The receptor binding assays for II-IV revealed that their selectivity had increased towards hsst2 and hsst5, but decreased towards hsst4 in comparison to I. In addn., this work also described the synthesis of sulfur-contg. building units, such as Acm-S-CH2CH2N(Fmoc)CH2CO2H (Acm = acetamidomethyl), for incorporation into peptides as groups capable of forming disulfide bridges.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:783790 HCAPLUS

DOCUMENT NUMBER: 136:151429

TITLE: A bioactive somatostatin analog without a type II' .beta.-turn: synthesis and conformational analysis in solution

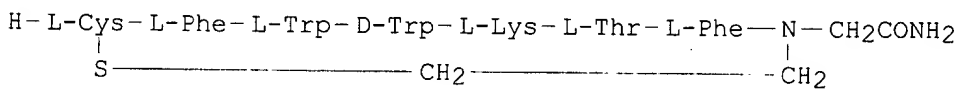
AUTHOR(S): Jiang, Shaokai; Gazal, Sharon; Gelerman, Gary; Ziv, Ofer; Karpov, Olga; Litman, Pninit; Bracha, Moshe; **Afargan, Michael**; Gilon, Chaim; Goodman, Murray

CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, USA

SOURCE: Journal of Peptide Science (2001), 7(10), 521-528, 2 plates
CODEN: JPSIEI; ISSN: 1075-2617

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A cyclic somatostatin analog I has been synthesized. Biol. assays show that this compd. has strong binding affinities to somatostatin hsst2 and hsst5 receptor subtypes (5.2 and 1.2 nM, resp., and modest affinity to hsst4 (41.1 nM)). Our conformational anal. carried out in DMSO-d6 indicates that this compd. exists as two structures arising from the trans and cis configurations of the peptide bond between Phe7 and N-alkylated Gly8. However, neither conformer exhibits a type II' .beta.-turn. This is the first report of a potent bioactive somatostatin analog that does not exhibit a type II' .beta.-turn in soln. Mol. dynamics simulations (500 ps) carried out at 300 K indicate that the backbone of compd. I is more flexible than other cyclic somatostatin analogs formed by disulfide bonds.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:607431 HCAPLUS
DOCUMENT NUMBER: 135:313821
TITLE: A novel somatostatin analogue prevents early renal complications in the nonobese diabetic mouse
AUTHOR(S): Landau, Daniel; Segev, Yael; **Afargan, Michel**; Silbergeld, Aviva; Katchko, Leonid; Podshyvalov, Andrey; Phillip, Moshe
CORPORATE SOURCE: Department of Pediatrics and Pathology, Laboratory of Molecular Endocrinology, University of the Negev, Beer Sheva, Israel
SOURCE: Kidney International (2001), 60(2), 505-512
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PTR-3173 (S) is a novel somatostatin analog that has been found to exert a prolonged inhibitory action on the growth hormone (GH)-insulin-like growth factor (IGF)-I axis, but not on insulin secretion. The authors investigated the potential effect of this agent on the development of markers of diabetic nephropathy in the nonobese diabetic (NOD) mouse model of insulin-dependent diabetes. Female diabetic NOD mice treated with PTR-3173 (DS group) or saline (D) and their control groups of nonhyperglycemic age-matched littermates (C) and C mice treated with PTR-3173 (CS) were sacrificed 3 wk after onset of diabetes. Serum GH was elevated in the D group, decreased in the DS group, and unchanged in the CS group. Serum IGF-I was significantly decreased in both the D and DS groups. Kidney wt., glomerular vol., albuminuria, and creatinine clearance were increased in the D animals and showed a trend toward normalization in the DS animals. Renal extractable IGF-I protein and IGFBP1 mRNA were increased in the D group and normalized in the DS group. GH antagonism by PTR-3173 has a blunting effect on renal/glomerular hypertrophy, albuminuria, and glomerular filtration rate (GFR) in diabetic NOD mice. This phenomenon is apparently assocd. with the prevention of renal IGF-I accumulation. Thus, modulation of GH effects may have beneficial therapeutic implications in diabetic nephropathy.

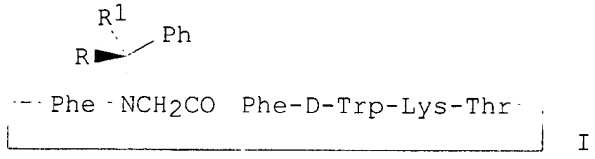
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:51142 HCAPLUS
DOCUMENT NUMBER: 134:95704
TITLE: Novel long-acting somatostatin analog with endocrine selectivity: potent suppression of growth hormone but not of insulin
AUTHOR(S): **Afargan, Michel**; Janson, Eva Tiensuu; Gelerman, Garry; Rosenfeld, Rakefet; Ziv, Offer; Karpov, Olga; Wolf, Amnon; Bracha, Moshe; Shohat, Dvira; Liapakis, George; Gilon, Chaim; Hoffman, Amnon; Stephensky, David; Oberg, Kjell
CORPORATE SOURCE: Peptor Ltd., Kiryat Weizmann, Rehovot, 76326, Israel
SOURCE: Endocrinology (2001), 142(1), 477-486
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Somatostatin, also known as somatotropin release-inhibiting factor (SRIF), is a natural cyclic peptide inhibitor of pituitary, pancreatic, and gastrointestinal secretion. Its long-acting analogs are in clin. use for treatment of various endocrine syndromes and gastrointestinal anomalies. These analogs are more potent inhibitors of the endocrine release of GH, glucagon, and insulin than the native SRIF; hence, they do not display considerable physiol. selectivity. Our goal was to design effective and physiol. selective SRIF analogs with potential therapeutic value. We employed an integrated approach consisting of screening of backbone cyclic peptide libraries constructed on the basis of mol. modeling of known SRIF agonists and of high throughput receptor binding assays with each of the five cloned human SRIF receptors (hsst1-5). By using this approach, we identified a novel, high affinity, enzymically stable, and long-acting SRIF analog, PTR-3173, which binds with nanomolar affinity to human SRIF receptors hsst2, hsst4, and hsst5. The hsst5 and the rat sst5 (rsst5) forms have the same nanomolar affinity for this analog. In the human carcinoid-derived cell line BON-1, PTR-3173 inhibits forskolin-stimulated cAMP accumulation as efficiently as the drug octreotide, indicating its agonistic effect in this human cell system. In hormone secretion studies with rats, we found that PTR-3173 is 1000-fold and more than 10,000-fold more potent in inhibiting GH release than glucagon and insulin release, resp. These results suggest that PTR-3173 is the first highly selective somatostatinergic analog for the in vivo inhibition of GH secretion, with minimal or no effect on glucagon and insulin release, resp.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:446757 HCAPLUS
DOCUMENT NUMBER: 129:175956
TITLE: Design, Synthesis, and Biological Activities of Potent and Selective Somatostatin Analogs Incorporating Novel Peptoid Residues
AUTHOR(S): Tran, Thuy-Anh; Mattern, Ralph-Heiko; **Afargan, Michel**; Amitay, Oved; Ziv, Ofer; Morgan, Barry A.; Taylor, John E.; Hoyer, Daniel; Goodman, Murray
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California at San Diego, La Jolla, CA, 92093-0343, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(15), 2679-2685
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society

No Date No Good

DOCUMENT TYPE: Journal
LANGUAGE: English
GI




I

AB The authors report the synthesis, bioactivity, and structure-activity relationship studies of compds. I (R = R1 = H; R = Me, R1 = H; R = H, R1 = Me), related to the Merck cyclic hexapeptide cyclo(Pro6-Phe7-D-Trp8-Lys9-Thr10-Phe11), L-363,301 (the numbering in the sequence refers to the position of the residues in native somatostatin). The Pro residue in L-363,301 is replaced with arylalkyl peptoid residues. The authors present a novel approach utilizing .beta.-Me chiral substitutions to constrain the peptoid side-chain conformation. These studies led to mols. which show potent binding and increased selectivity to the hsst2 receptor (weaker binding to the hsst3 and hsst5 receptors compared to L-363,301). In vivo, these peptoid analogs selectively inhibit the release of growth hormone but have no effect on the inhibition of insulin. The biol. assays which include binding to five recombinant human somatostatin receptors carried out in two independent labs. and in vivo inhibition of growth hormone and insulin provide insight into the relationship between structure and biol. activity of somatostatin analogs. These results have important implications for the study of other peptide hormones and neurotransmitters.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:595005 HCAPLUS
DOCUMENT NUMBER: 121:195005
TITLE: Differential effects of various antiinflammatory drugs on theophylline neurotoxicity
AUTHOR(S): Hoffman, Amnon; **Afargan, Mishel**; Pinto, Evelyne; Gilhar, Dalia; Backon, Joshua
CORPORATE SOURCE: Sch. Pharm., Hebrew Univ. Jerusalem, Jerusalem, 91120, Israel
SOURCE: Pharmacology, Biochemistry and Behavior (1994), 49(2), 335-9
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of the present investigation was to evaluate whether antiinflammatory drugs affect the pharmacodynamics of theophylline-induced seizures. Adult male Lewis rats were treated with either dexamethasone (DEX), hydrocortisone (HYD), ibuprofen (IBU), or mefenamic acid (MFA), for 4 consecutive days. On the fourth day they received a const. infusion of theophylline (2 mg/min IV) until the onset of maximal seizures. Then, blood and cerebrospinal fluid (CSF) were obtained for theophylline concn. detns. by HPLC. It was found that pretreatment with the corticosteroids DEX and HYD elevated the CSF theophylline concn. required to induce maximal seizures in comparison to the untreated rats (242 .+-. 6, 232 .+-. 6, and 203 .+-. 10 mg/L, resp., n = 10, $p < 0.05$). MFA also increased the CSF theophylline concn. at that end-point in comparison to the controls ($p < 0.01$), whereas pretreatment with IBU had no effect (280 .+-. 10 MFA, 225 .+-. 9 IBU vs. 220 .+-. 8 controls, n = 12). The data suggests that

concomitant treatment with antiinflammatory drugs, together with theophylline, do not increase the risk for theophylline-induced seizures. Moreover, in certain cases they may elevate the seizure threshold and protect against these hazardous episodes.

L2 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:182368 HCAPLUS
DOCUMENT NUMBER: 120:182368
TITLE: Cyclosporine enhances theophylline neurotoxicity in rats
AUTHOR(S): Hoffman, Amnon; Pinto, Evelyne; **Afargan, Mishel**; Schattner, Amichai
CORPORATE SOURCE: Sch. Pharm., Hebrew Univ., Jerusalem, 91120, Israel
SOURCE: Journal of Pharmaceutical Sciences (1994), 83(4), 559-61
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Treatment with cyclosporine may be assocd. with adverse central nervous system (CNS) effects as well as with the potentiation of effects of certain other drugs. In particular, theophylline-induced seizures, which are often fatal and occur unpredictably over a wide range of serum theophylline concns., may be pptd.. To study this interaction, adult rats that were injected with cyclosporine or placebo (50 mg/kg in a single dose or on each of four consecutive days) received a const. infusion of theophylline (2 mg/min i.v.) until the onset of maximal seizures. At that time, blood, cerebrospinal fluid (CSF), and brain tissue samples were obtained for theophylline concn. detns. by HPLC, as well as for measurement of several biochem. parameters in the serum. Consecutive cyclosporine administration (but not a single dose) reduced serum protein levels. There was a small increase in theophylline sensitivity after a single dose of cyclosporine. The CSF theophylline concns. at the onset of seizures were 215 vs 202 mg/L; however, sequential cyclosporine treatment resulted in significant lowering of the CSF theophylline concns. required to produce convulsions (231 vs 191). Likewise, the drug concns. at the onset of convulsions in both the brain and serum were significantly lower in cyclosporine-treated rats than in control animals. Thus, cyclosporine treatment may be a predisposing factor for theophylline toxicity and increase the risk for generalized seizures.

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L3 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:536576 HCAPLUS

DOCUMENT NUMBER: 137:241819
TITLE: Toward a PKB Inhibitor: Modification of a Selective PKA Inhibitor by Rational Design
AUTHOR(S): Reuveni, Hadas; Livnah, Nurit; Geiger, Tamar; Klein, Shoshana; Ohne, Osnat; Cohen, Ilana; Benhar, Moran; **Gellerman, Gary**; Levitzki, Alexander
CORPORATE SOURCE: Department of Biological Chemistry, The Silverman Institute of Life Sciences, Hebrew University of Jerusalem, Jerusalem, Israel
SOURCE: Biochemistry (2002), 41(32), 10304-10314
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein kinase B/Akt (PKB) is an anti-apoptotic protein kinase that has strongly elevated activity in human malignancies. We therefore initiated a program to develop PKB inhibitors, "Aktstatins". We screened about 500 compds. for PKB inhibitors, using a radioactive assay and an ELISA assay that we established for this purpose. These compds. were produced as combinatorial libraries, designed using the structure of the selective PKA inhibitor H-89 as a starting point. We have identified a successful lead compd., which inhibits PKB activity in vitro and in cells overexpressing active PKB. The new compd. shows reversed selectivity to H-89: In contrast to H-89, which inhibits PKA 70 times better than PKB, the new compd., NL-71-101, inhibits PKB 2.4-fold better than PKA. The new compd., but not H-89, induces apoptosis in tumor cells in which PKB is amplified. We have identified structural features in NL-71-101 that are significant for the specificity and that can be used for future development and optimization of PKB inhibitors.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:203445 HCAPLUS
DOCUMENT NUMBER: 136:386388
TITLE: Synthesis of novel protected N.alpha.(.omega.-thioalkyl) amino acid building units and their incorporation in backbone cyclic disulfide and thioetheric bridged peptides
AUTHOR(S): Gazal, S.; **Gellerman, G.**; Glukhov, E.; Gilon, C.
CORPORATE SOURCE: Department of Organic Chemistry, Hebrew University, Jerusalem, Israel
SOURCE: Journal of Peptide Research (2001), 58(6), 527-539
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB General methods for the prepn. of protected N.alpha.(.omega.-thioalkyl) amino acids building units for backbone cyclization using reductive alkylation and on-resin prepn. are described. The synthesis of non-Gly Fmoc-protected S-functionalized N-alkylated amino acids is based on the reaction of readily prepd. protected .omega.-thio aldehyde with the appropriate amino acid. Prepn. of Fmoc-protected S-functionalized N-alkylated Gly building units was carried out using two methods: reaction of glyoxylic acid with Acm-thioalkylamine and an on-resin reaction of bromoacetyl resin with Trt-thioalkylamines. Three model peptides were prepd. using these building units. The GlyS2 building unit was incorporated into a backbone cyclic analog of somatostatin that contains a disulfide bridge. Formation of the disulfide bridge was performed by on-resin oxidn. using I2 or TI(CF3COO-)3. Both methods resulted in the desired product in a high degree of purity in the crude. The AspS3 building unit was also successfully incorporated into a model peptide. In

addn., the in situ generation of sulfur contg. Gly building units was demonstrated on a Substance P backbone cyclic analog contg. a thioether bridge.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:296349 HCAPLUS
DOCUMENT NUMBER: 135:77069
TITLE: Facile synthesis of orthogonally protected amino acid building blocks for combinatorial N-backbone cyclic peptide chemistry
AUTHOR(S): **Gellerman, G.**; Elgavi, A.; Salitra, Y.; Kramer, M.
CORPORATE SOURCE: Peptor Ltd, Rehovot, 76326, Israel
SOURCE: Journal of Peptide Research (2001), 57(4), 277-291
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:77069
AB Protected N.alpha.-(aminoallyloxycarbonyl) and N.alpha.-(carboxyallyl) derivs. of all natural amino acids (except proline), and their chiral inverters, were synthesized using facile and efficient methods and were then used in the synthesis of N.alpha.-backbone cyclic peptides. Synthetic pathways for the prepn. of the amino acid building units included alkylation, reductive amination and Michael addn. using alkylhalides, aldehydes and .alpha.,.beta.-unsatd. carbonyl compds., and the corresponding amino acids. The resulting amino acid prounits were then subjected to Fmoc protection affording optically pure amino acid building units. The appropriate synthetic pathway for each amino acid was chosen according to the nature of the side-chain, resulting in fully orthogonal trifunctional building units for the solid-phase peptide synthesis of small cyclic analogs of peptide loops (SCAPLs). N.alpha.-amino groups of building units were protected by Fmoc, functional side-chains were protected by t-Bu/Boc/Trt and N-alkylamino or N-alkylcarboxyl were protected by Alloc or Allyl, resp. This facile method allows easy prodn. of a large variety of amino acid building units in a short time, and is successfully employed in combinatorial chem. as well as in large-scale solid-phase peptide synthesis. These building units have significant advantage in the synthesis of peptido-related drugs.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:894549 HCAPLUS
DOCUMENT NUMBER: 134:208088
TITLE: In situ generation of Fmoc amino acid chlorides for extremely difficult couplings to sterically hindered secondary amines in solid-phase peptide synthesis
AUTHOR(S): Falb, Eliezer; Yechezkel, Tamar; Salitra, Yosphe; **Gellerman, Gary**; Muller, Dan; Gilon, Chaim
CORPORATE SOURCE: Peptor Ltd., Rehovot, 76326, Israel
SOURCE: Peptides for the New Millennium, Proceedings of the American Peptide Symposium, 16th, Minneapolis, MN, United States, June 26-July 1, 1999 (2000), Meeting Date 1999, 55-57. Editor(s): Fields, Gregg B.; Tam, James P.; Barany, George. Kluwer Academic Publishers: Dordrecht, Neth.
CODEN: 69ATHX
DOCUMENT TYPE: Conference
LANGUAGE: English

AB A symposium report. Bis(trichloromethyl)carbonate (BTC) is used to generate, in-situ, Fmoc-amino acid chlorides for their use in difficult peptide coupling reactions in solid-phase peptide synthesis.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:763934 HCAPLUS
DOCUMENT NUMBER: 123:218394
TITLE: Tumor and other cell growth- and differentiation-related biological applications of alkaloids derived from the tunicate Eudistoma sp., and purifn., characterization, and synthesis of compds.
INVENTOR(S): Spector, Ilan; Shochet, Nava R.; Kashman, Yoel; Rudi, Amira; **Gellerman, Gary**
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA
SOURCE: U.S., 42 pp. Cont.-in-part of U.S. 5,278,168.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5432172 | A | 19950711 | US 1993-28322 | 19930309 |
| US 5278168 | A | 19940111 | US 1992-924194 | 19920803 |
| WO 9403433 | A1 | 19940217 | WO 1993-US7201 | 19930730 |
| W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9349957 | A1 | 19940303 | AU 1993-49957 | 19930730 |

PRIORITY APPLN. INFO.:
US 1992-924194 A2 19920803
US 1993-28322 A 19930309
WO 1993-US7201 W 19930730

AB Biol. applications of synthetic and natural alkaloids derived from the tunicate Eudistoma sp. are disclosed. A method regulating cell growth includes contacting one or more cells with an effective concn. of a compd. for regulating cell growth. These compds. include: Segoline A, Segoline B, Isosegoline A, Norosegoline, Debromoshermilamine, Eilatin, 4-methylpyrido[2,3,4-kl]acridine, pyrido[2,3,4-kl]acridine, 1-acetyl-2,6-dimethylpyrido[2,3,4-kl]acridine, and derivs. and combinations of these compds. An effective concn. range for using these compds. can range from approx. 0.1 .mu.M to 100 .mu.M. The effective concn. range for Eilatin, the most potent of these compds. is from 0.01 .mu.M to 0.99 .mu.M, and the effective concn. range for the other compds. of the present invention is from about 1.0 .mu.M to 100 .mu.M. The method has been shown to suppress growth of tumor cells, to induce differentiation of the tumor cells, and induce reverse transformation of the tumor cells. In transformed cells, the method induces reverse transformation. The method also inhibits the proliferation of cells. The examples show that the method of the present invention affects cAMP-mediated biol. processes. At the effective concns. of the compds., this method affects the cAMP-mediated biol. processes of cells to achieve the results described above. Isolation, purifn., and characterization of the Eudistoma alkaloids are described, as are derivatization and chem. transformation, biol. and biochem. studies, and biomimetic synthesis of pyrido[k,l]acridines and of Eilatin.

L3 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:743917 HCAPLUS
DOCUMENT NUMBER: 123:160277
TITLE: Potent antileukemic activity of the novel agents norsegoline and dibezine
AUTHOR(S): Einat, Michal; Nagler, Arnon; Lishner, Michael; Amiel, Aliza; Yarkoni, Shai; Rudi, Amira; **Gellerman, Gary**; Kashman, Yoel; Fabian, Ina
CORPORATE SOURCE: Department Cell Biology Histology, Tel Aviv University, Tel Aviv-Jaffa, 69978, Israel
SOURCE: Clinical Cancer Research (1995), 1(8), 823-9
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of norsegoline, a natural marine product, and dibezine, a synthetic product, on the survival of human myeloid progenitor cells [colony-forming unit-cells (CFU-C)] from normal individuals and from 10 patients with Philadelphia-pos. chronic myelogenous leukemia (CML) in chronic phase and blastic crisis were examd. and their effects were compared to the effect of IFN-.alpha.. Results indicate that norsegoline and dibezine have in vitro an antileukemic effect against Philadelphia-pos. cells and may be used in conjunction with currently available agents for ex vivo purging of BM and/or peripheral blood of CML patients in conjunction with autologous bone marrow transplantation.

L3 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:224760 HCAPLUS
DOCUMENT NUMBER: 122:133489
TITLE: The biomimetic synthesis of marine alkaloid related pyrido- and pyrrolo[2,3,4-k]acridines
AUTHOR(S): **Gellerman, Gari**; Rudi, Amira; Kashman, Yoel
CORPORATE SOURCE: School of Chemistry, Tel Aviv Univ., Ramat Aviv, 69978, Israel
SOURCE: Tetrahedron (1994), 50(45), 12959-72
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 122:133489
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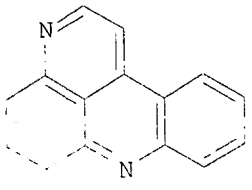

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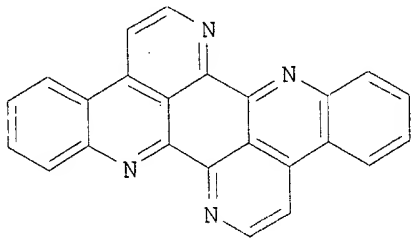

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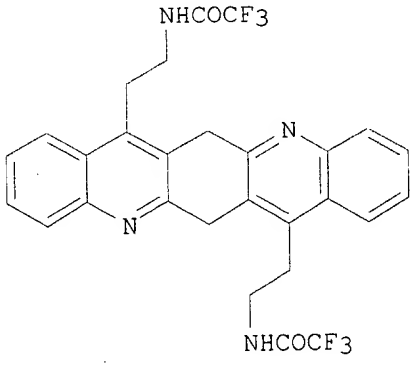

III

AB A biomimetic reaction between .beta.,.beta.'-diaminoketones (e.g. kynuramine, kynurenine or o,o'-diaminobenzophenone) and a variety of cyclohexanediones and quinones leading to pyrido[2,3,4-kl]acridines is described. The synthesis of several di- and tetrahydropyrido[2,3,4-kl]acridine derivs., e.g. I, as well as benzoderivatives of the marine alkaloids eilatin and ascididemin has been accomplished. Addnl., the new heterocycles isoeilatin (II), and diazepentacene III have also been synthesized. All newly prepd. heterocycles have been fully characterized by IR, mass spectra and mainly by NMR spectroscopy. An analogous synthesis has been developed for pyrrolo[2,3,4-kl]acridines, the heterocyclic core of the bioactive marine alkaloids the plankinidines.

L3 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:557945 HCAPLUS
DOCUMENT NUMBER: 121:157945
TITLE: Preparation of Eudistoma alkaloids as neoplasm inhibitors
INVENTOR(S): Spector, Ilan; Shochet, Nava R.; Kashman, Yoel; Rudi, Amira; **Gellerman, Gary**
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 9403433 | A1 | 19940217 | WO 1993-US7201 | 19930730 |

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RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,

BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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| US 5278168 | A | 19940111 | US 1992-924194 | | 19920803 |
| US 5432172 | A | 19950711 | US 1993-28322 | | 19930309 |
| AU 9349957 | A1 | 19940303 | AU 1993-49957 | | 19930730 |
| PRIORITY APPLN. INFO.: | | | US 1992-924194 | A2 | 19920803 |
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OTHER SOURCE(S): MARPAT 121:157945
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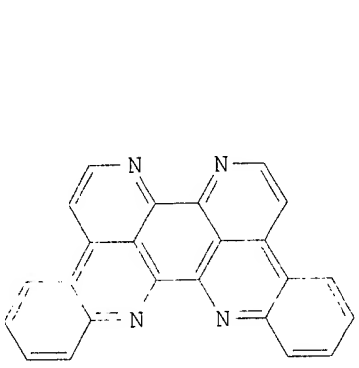

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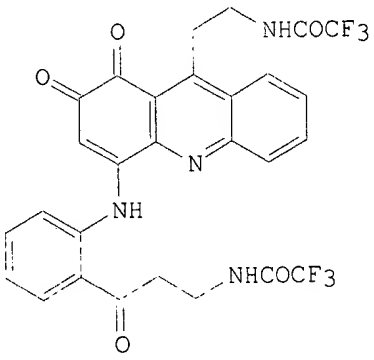

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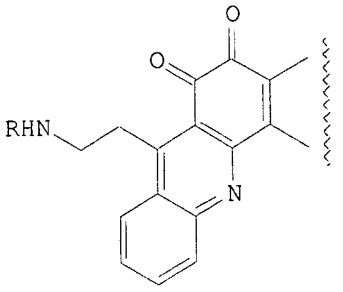

III

AB Biol. applications of synthetic and natural alkaloids derived from the tunicate Eudistoma sp., as well as the prepn. of synthetic pyridoacridines, and methods for the synthesis of Eilatin are disclosed. These compds. include: Segoline A, Segoline B, Isosegoline A, Norosegoline, Debromoshermilamine, Eilatin (I), 4-methylpyrido[2,3,4-kl]acridine, pyrido[2,3,4-kl]acridine, 1-acetyl-2,6-dimethylpyrido[2,3,4-kl]acridine, and derivs. and combinations of these compds. Thus, 2-(H2N)C6H4COCH2CH2NHCOCF3 was cyclocondensed with catechol in the presence of NaIO3 to give acridinedione II which was treated with BF3.Et2O to give III (R = COCF3). The latter was treated with NH3/MeOH to give I. Data for biol. activity of title compds. were given in graphic form.

L3 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2003 ACS

| | |
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| ACCESSION NUMBER: | 1994:323977 HCAPLUS |
| DOCUMENT NUMBER: | 120:323977 |
| TITLE: | Biomimetic synthesis of ascididemin and derivatives |
| AUTHOR(S): | **Gellerman, Gari**; Rudi, Amira; Kashman, Yoel |
| CORPORATE SOURCE: | Sch. Chem., Tel Aviv Univ., Tel Aviv, 69978, Israel |
| SOURCE: | Synthesis (1994), (3), 239-41 |
| | CODEN: SYNTBF; ISSN: 0039-7881 |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |
| OTHER SOURCE(S): | CASREACT 120:323977 |

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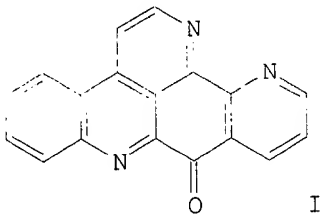
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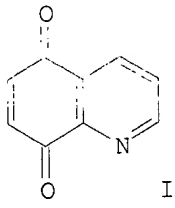
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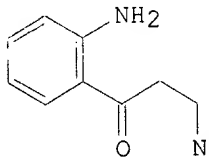
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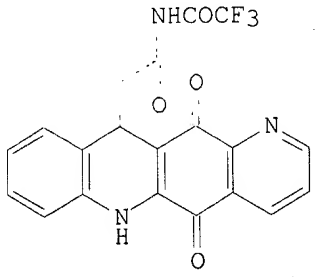
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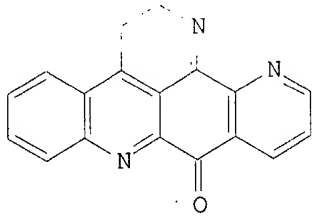
V

AB A two-step biomimetic synthesis of the pentacyclic pyrido[2,3,4-kl]acridine marine alkaloid ascididemin (I) from quinolinequinone II and N-trifluoroacetamidokynuramine (III) was achieved. The crucial step (IV to V) involves the simultaneous formation of two pyridine rings in a process which might well offer an explanation for the biogenetic synthesis in marine organisms. The prepn. of substituted ascididemins by either starting from substituted quinoline-quinones to afford 11-methoxyascididemin, or by nitration of to the mono 1- or 3-nitroascididemins was achieved.

L3 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2003 ACS

| | |
|---|---|
| ACCESSION NUMBER: | 1993:428417 HCAPLUS |
| DOCUMENT NUMBER: | 119:28417 |
| TITLE: | A two step biomimetic total synthesis of eilatin |
| AUTHOR(S): | **Gellerman, Gari**; Babad, Malca; Kashman, Yoel |
| CORPORATE SOURCE: | Sch. Chem., Tel Aviv Univ., Tel Aviv, 69978, Israel |
| SOURCE: | Tetrahedron Letters (1993), 34(11), 1827-30 |
| | CODEN: TELEAY; ISSN: 0040-4039 |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |
| OTHER SOURCE(S): | CASREACT 119:28417 |

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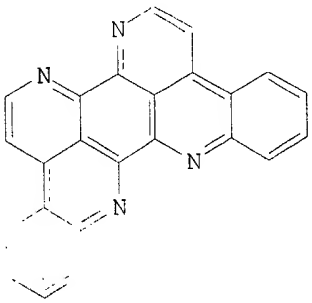
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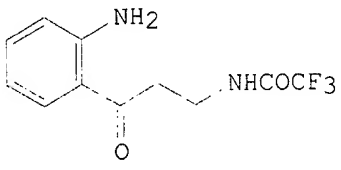
II

AB The sym. tetraaza heptacyclic alkaloid eilatin (I) was synthesized in a biomimetic two step reaction from catechol and trifluoroacetylkynuramine (II) under oxidative conditions in the first step (aq. EtOH, NaIO3) and basic conditions (ammoniacal MeOH, DMAP) in the second. Two other unsuccessful approaches, one leading to 7-phenylascididemin, are described.

L3 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:428416 HCAPLUS
DOCUMENT NUMBER: 119:28416
TITLE: Biomimetic synthesis of pyrido[2,3,4-k,l]acridines
AUTHOR(S): **Gellerman, Gari**; Rudi, Amira; Kashman, Yoel
CORPORATE SOURCE: Sch. Chem., Tel Aviv Univ., Tel Aviv, 69978, Israel
SOURCE: Tetrahedron Letters (1993), 34(11), 1823-6
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 119:28416
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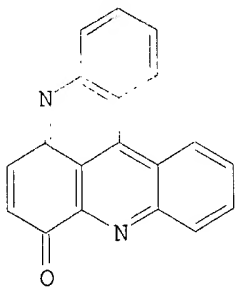


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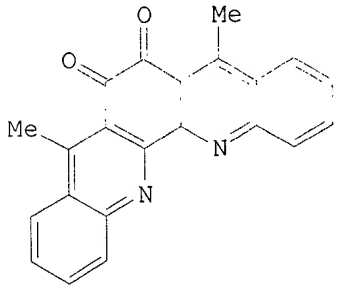


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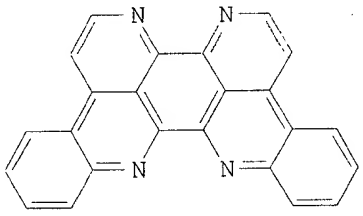


III

AB A short new biomimetic route to the pyrido[2,3,4-kl]acridine ring system has been developed from readily available benzoquinone, or hydroquinone precursors, and .beta.,.beta.'-diaminoketones like kynuramine (2-H2NC6H4COCH2CH2NH2) or 2,2'-diaminobenzophenone, involving one key step. Pyrido[2,3,4-kl]acridine and closely related compds., e.g. I, were prepd. The reaction has been shown to proceed to the formation of 1:1 and/or 1:2 quinone/amine adducts. Using of o-aminoacetophenone afforded dibenzo[1,10]phenanthrolinedione (II) a potential intermediate to eilatin (III).

L3 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:651608 HCAPLUS
DOCUMENT NUMBER: 117:251608
TITLE: Synthesis of pyrido[2,3,4-kl]acridines. A building block for the synthesis of pyridoacridine alkaloids
AUTHOR(S): **Gellerman, Gari**; Rudi, Amira; Kashman, Yoel
CORPORATE SOURCE: Sch. Chem., Tel Aviv Univ., Tel Aviv-Jaffa, 69978, Israel

SOURCE: Tetrahedron Letters (1992), 33(38), 5577-80
CODEN: TELEAY; ISSN: 0040-4039

DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 117:251608
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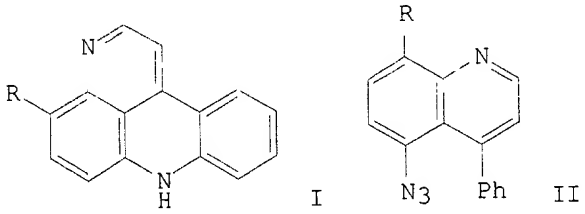

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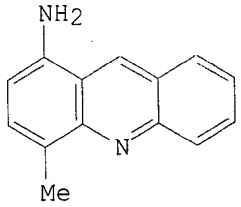

III

AB Two new syntheses have been developed for the prepn. of substituted pyrido[2,3,4-kl]acridines, e.g. I (R = Me, H). The first synthesis involves a Skraup reaction and a nitrene insertion of isoquinoline II, whereas the second includes a new pyridine ring synthesis starting from a 1-amino group on acridine III and taking advantage of the 9-position of the latter heterocycle.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 18 JUN 2003 HIGHEST RN 533863-98-8
DICTIONARY FILE UPDATES: 18 JUN 2003 HIGHEST RN 533863-98-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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     N.alpha.-(3-aminopropyl)-, (1.fwdarw.9)-lactam, cyclic
     (2.fwdarw.7)-disulfide (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   PTR 3205
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  9
NTE  modified (modifications unspecified)
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stereo          Trp-4         -           D
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